T H E S I S

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on

THE INTERNAL SECRETIONS of the FEMALE GENERATIVE ORGANS - With EXPERIMENTAL ENQUIRY into the SECRETIONS of the UTERUS and TUBES in RABBITS.

by

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I N D E X .

PREFACE.

My interest in the subject of the Internal Secretions, and particularly those of the generative organs in the female, has been aroused by the observation of clinical cases, after removal of ovaries, in which menstruation recurred, and also in a case in which, after double ovariotomy and sub-total hysterectomy, there was a regular and excessive discharge of blood from the lining of the cervix, which recurred with definite periodicity, and was unaffected by any drugs, until I tried corpora lutea. On looking up the literature of the subject, I came across Bond's paper, as also that of Blair Bell, dealing with the correlation of ovaries and womb, the views expressed being diametrically opposed. Bond also touched on the question of the saline secretion of the mucosa of the tubes and womb, and I determined that as I had the opportunity to do some experimental work, that I would check some of his observations, particularly such as dealt with the ovarian influence on the changes and function of the uterine/

uterine mucosa, with special reference to the secretion of the saline fluid.

My observations will, I hope, form some small contribution, however slight, to our knowledge of the subject, which bears so intimately on operative gynecological treatment.

The experiments are some of a series conducted at the Laboratory of the Royal College of Physicians, Edinburgh, between November 1910 and February 1913.

I desire to express my thanks to the President and Fellows of the College for the permission to carry out this work, and also my great appreciation of the kindly assistance and help afforded by the Superintendent and all the Staff.

THE/

THE INTERNAL SECRETIONS OF THE FEMALE GENERATIVE ORGANS

With Experimental enquiry into the SECRETIONS of TUBES & UTERUS, &C., ITS NATURE & FUNCTION and THE EFFECT OF THE OVARY ON IT.

I N T R O D U C T I O N .

SECRETIONS of UTERUS and TUBES.

Up to the present time although much work has been done on the internal secretions, very little definite information is known of the internal secretions of the female generative organs, and little, if anything, has been done on the secretion of the endometrium and tubal lining membrane.

Text Books on Medicine, Physiology, Obstetrics, and Gynecology say little or nothing on the subject, and although it has been long recognised that in all the Mammalia the free secretion of fluid by the lining membrane of the womb, during pregnancy takes place, which is considered both protective to the/

the life of the young ovum and of nutritive value, yet no attempt seems to have been made to account for the origin of this, nor of the nature and function of the saline fluid which continuously bathes the internal surface of the Tubes and Womb, and no reference made to it, so far as I know, excepting in a paper by Bond, dealing with "Certain features of the Secretory Activity of the Uterus and Fallopian Tubes".

Text books on Physiology when dealing with the histology of the Uterus and Tubes make no reference to the secretions which continuously bathe the mucous membrane and are probably secreted by it.

Works on Gynecology while dealing with the normal secretions of the Vagina, make no reference to those of the Uterus. Recently, however, Blair Bell has suggested that menstruation is dependent upon and brought about by a secretion of the Uterine mucosa - and Young's investigations regarding the structure of the mucosa, and its changes during menstruation and pregnancy, have led to his advancing an imbibition theory, whereby the cells of the stroma take up fluid freely, this fluid probably coming from the blood vessels, possibly also from the extra secretion/

secretion of the normal saline fluid, which in the rabbit at any rate, is always present. Apart from the above, I am unable to find any records of work done, bearing on the physiological relationship of the Tubes and Uterus, and their secretions, to the bodily economy generally, though Bond, in his paper records some experimental work, relative to the effect of these parts on the ovaries, and later Marshall & Carmichael gave the results of hysterectomy in young rabbits, on the development of the Ovaries, and found in every instance that the ovaries were unaffected.

THEORY of INTERNAL SECRETIONS.

Although, as yet, we have much speculation and hypothesis, and very little definite knowledge, the theory is, that certain structures in the body, chiefly glandular, and both with and without excretory ducts, secrete substances which are absorbed by the blood or lymphatics, and have an important influence on the metabolism of the body, and are often essential to life itself. It is assumed, that the substances so secreted, act like hormones, as in the manner/

manner of the secretion of the pancreas. Bayliss & Starling have shown by their researches, that this depends for its activity on the development in the duodenum - under the influence of acids - of a substance secretin from pro secretin (rather than upon reflex nervous stimuli). This substance, when absorbed, causes a copious flow of pancreatic juice.

It is upon the efficient supply of these internal substances that the maintenance of good health depends, thus the necessity of the various organs which furnish them being in a healthy condition, so that the individual may be well fitted to combat and resist the invasion of disease. For there is no doubt that all disease is preceded by a disturbed nutrition, local or general, and that this disturbance in turn depends on a departure from normal of the blood plasma, owing to a reduction in its enzymes and ferments derived from the alimentary canal through the portal stream. The leucocytes absorb the pancreatic and splenic secretions, and carry them by the blood stream throughout the body to the tissues. The ferments strengthen phagocytic action and when carried to the body tissue cells, stimulate their transforming activities. Deficient internal ferments and/

and secretions thus mean a lessened phagocytosis and lessened resistance to disease. Pavy holds that the enzymes are dual bodies, one portion is insoluble in alcohol and indestructible by heat, and is probably a protein: the other - the co-ferment or activator - is usually soluble in alcohol, diffusible, and can be boiled without losing its properties, and corresponds with the active agents as obtained from the Thyroid and Suprarenal capsule.

Enzymes have the property possessed by extracts of organs, of stimulating the functional activity of the organs from which they are obtained. The assumption from the above follows that a physiologically perfect blood plasma should provide immunity.

The processes of metabolism are probably chiefly dependent on enzyme action, and some transformations which take place in the body are most readily explained on the ground of reversibility of enzyme action, as shown by H.C.Sherman.

If the digestive enzymes are not doing their work normally, then the body is open to the inroads of disease. These enzymes are particularly deficient or absent in digestive disorders, and thus toxines accumulate, and this furnishes the key to Metchnikoff's theory and assertion that most of the diseases/

diseases of old age are dependent on intestinal toxines, these acting deleteriously, because of the deficient action of the ferments. In normal digestion one of the most important effects is the destruction of disease germs, the successive chemical changes from alkaline to acid, and then to alkaline again, very seriously hinders, if it does not prevent, germ proliferation. If the germs are not destroyed in the intestinal wall, they are next met by the phagocytes of the white blood cells.

It was shown by Stohr and A.B.McCallum that phagocytes constantly leave the blood, pass through the intestinal wall into the lumen of the gut, pick up bacteria and carry them back into the circulation. On the introduction of foreign bodies, say bacteria, into the body of an animal, there usually ensues a flow of lymph to the part which is quickly followed by an incursion of large numbers of white blood cells which seize upon and ultimately digest the bacteria. If the number and avidity of these corpuscles are sufficient, the infection is suppressed, but if, from the number or rapidity of multiplication of the bacteria, they are too many for the white blood cells, then infection ensues, which remains local or becomes general. But, as the phagocytosis depends on the ferments/

ferments and enzymes which they contain, the protection of the body really depends on the secretions being regularly and freely furnished to the blood.

It seems, therefore, that the working out of the theory of internal secretions is the greatest advance of modern medicine, and, though observers are not entirely at one in the interpretation of results obtained, there is sufficient data to encourage the belief, that the more fully the individual glands and organs are studied, the more likely are we to obtain an explanation of the involved questions of resistance to and immunity from microbic invasion.

Sir Almroth Wright has done good work in regard to the study of the changes in the blood plasma, as produced by the organisms of disease, and helped to lay the foundation for the scientific treatment by means of Vaccines. Still, preventive medicine is always to be preferred to curative, and to be worthy the name must be able to render the individual proof against attack, and this can only be done by accurate knowledge of the various constituents of the blood plasma of an absolutely physiologically perfect individual, in whom all the glands and tissues are secreting and functioning efficiently, and pouring/

pouring their contents into the blood. It is thus to physiological, rather than to pathological research that one must turn for information.

C.E. de M. Sajous says:- "The leucocytes " secrete their intracellular trypsin into the " blood plasma, thus endowing the latter with its " bactericidal property, and the power to raisethe " anti-bacterial power of the blood, with respect " to an invading microbe, is out of all comparison " the most valuable asset in medicine".

While, therefore, at the present juncture of our knowledge, there can possibly be some objections urged against the too free use of vaccines and sera, obtained from the causal organisms of disease in the usual way, - by treating the growths on the various media - there can be no valid objection to the safety or rationality of the use of physiological solutions, as those of the juice of the spleen and red bone marrow, gastric juice, &c., - in accordance with the law that:- The extract of an organ has the power of stimulating the functional activity of that organ, and so combating bacterial and toxic invasion. It is upon this theory of the internal secretions that the present day system of Organotherapy or Opotherapy has been established.

Organotherapy, or treatment by animal secretions/

secretions and extracts, was practiced by the ancient physicians and by those of all ages. It is, indeed, as old as medicine itself, and, although it was used wholly empirically by the ancients, yet it gave results, which, in view of the degree to which the method obtained, must have been somewhat satisfactory. Hippocrates scientifically studied the efficiency of the various organs as remedies. Pliny, likewise, used testicular substance as an aphrodisiac. This form of treatment fell into disrepute and discredit, because of the abuses to which it lent itself, and no facts of any real value were known, until modern scientific investigation, and the epoch-making discovery of Claude Bernard 1867 and Brown-Sequard 1869 on the internal secretions of the glands, caused its revival.

Bernard announced his theory:-

"That certain structures of a glandular nature,
" the functions of which were then very improperly
" known, threw into the blood fluid substances which
" were essential to good health and in many instances
" to life itself".

Since this announcement of the importance of the subject, much good work has been done, and towards the end of the last century, when in 1885 Dr. G.R.Murray of Newcastle-on-Tyne, called attention to the/

the results of the exhibition of Sheep's Thyroid - we have seen the gradual building up of a new scientific organo-therapy founded on experimental medicine and physiology.

In 1889 Brown-Sequard again advocated the use of the extract of the testicles, as a cure for the various symptoms of impotence and old age. The results were disappointing, and the next revival of treatment by organic products, was that suggested by Regis in 1893, of the use of the Ovary to combat the mental disturbance following ovariotomy.

In 1894 Oliver and Schäfer directed attention to the use of supra-renal extract, and its action on blood pressure, and the same observers in 1896, were the first to study the secretion of the Pituitary. The pancreatic ferments were next studied and the results of the investigations of Bayliss & Starling appear. Subsequently, during the last 10 years, many investigations have amplified the foregoing, and in turn, almost all the glands have been studied, including the thymus, liver, and also the corpus luteum.

The valuable results obtained in medicine by the use of the Thyroid, amongst which one numbers the/

the most remarkable triumph over myxodema. Its value is also more extended in the treatment of cretinism, obesity, and in some cases of simple goitre. Opinions are, however, divided as to its indication, in the last mentioned trouble. In the malnutrition of infants Thyroid has given good results, and it is claimed to have a retarding influence, arresting and absorbing carcinomatous nodules. The evidence in this latter connection is somewhat fragmentary.

Almost as startling in its beneficial effects, is the exhibition of Supra-renal capsule, particularly in case of shock, and as a local and general constricting agent, in its effect on blood vessels. It has been used in numerous directions, and is of considerable benefit in asthma, especially such cases as are associated with lowered vasa motor tone.

Associated with cocain, it has been extensively used as a local anaesthetic, both for minor and some major operations by Donitz, who injected it into the spinal canal - and Gangitans has used the combination in thirty-one cases of hernia, and in excision of the upper jaw &c. Great care should be taken/

taken in patients with renal disease and arteriosclerosis. Also it is used largely, as an application to mucous surfaces, in laryngological and ophthalmological and rhinological operations. Oliver showed, that applied directly to blood vessels it has a constricting effect, and is, therefore, largely used in various hemorrhagic conditions.

Thelwall Thomas has used the drug in cases of Haemophilia. In purpura and haemoptysis, and post partum haemorrhage, it has arrested the bleeding.

Marricardi has used paragangline - a preparation of supra-renal - in case of gastro-intestinal atony with fermentation, which was arrested, probably due to increased motor activity and more adequate propulsion of the stomach contents.

Plessi and Baccarain thus conclude certain forms of gastro-intestinal dyspepsia depend on functional insufficiency of the supra-renals.

Cardiac disorders of a functional nature, and neurasthenia, with lowered arterial tension have been benefited by supra-renal.

Adrenalin has been found useful in cases of apparent death (Asphyxia, submersion and chloroform syncope). The treatment of Addison's disease, on the/

the assumption that its aetiology is disease of or perverted supra-renals has been disappointing. Many cases of Addison's disease show no supra renal lesion.

PITUITARY EXTRACT has given promising results in the treatment of collapse, owing to its powerful and lasting action on the circulatory system. It increases the force of the heart beat, and raises blood pressure. Its therapeutics, broadly speaking, hinge on its relationship to certain nutritional and circulatory disorders. It has thus been employed beneficially in acromegaly and gigantism, also in several cases of exophthalmic goitre, it having been maintained that the infundibular secretion is an antidote to excessive Thyroid action.

In paralysis agitans - the sleeplessness, perspiration or lowered blood pressure are improved. Cases of Cerebral anaemia, endocarditis, cardiac dilatation and arterio-sclerosis are all benefited by pituitrin. It is indicated in cases of Aortic disease where digitalis is condemned.

In all forms of haemorrhage, especially secondary haemorrhage after operation, and post partum haemorrhage, Pituitrin is invaluable, also in Menorrhagia and endometritis. I have used it most beneficially/

beneficially in shock of abdominal sepsis and in paresis of the gut with stasis of contents for the purpose of promoting intestinal contraction.

After laparotomies, Dr.Bidwell has found that Pituitrin will ensure action of the bowels with little or no added aperient, and in no case did the patient require catheterisation.

THE/

THE OVARY.

ANATOMY.

The ovaries are two ovoid - somewhat flattened - solid-looking bodies, lying one on each side of the pelvis, near the brim of the pelvis. They project from the posterior layer of the fold of peritoneum, which forms the broad ligament. The free surface which projects into the peritoneal cavity is uncovered by peritoneum. They are attached to the Uterus, at the cornua, by means of the ovarian ligaments, and a free edged fold of peritoneum runs from the gland on the right side to the appendix - Appendo-ovarium ligament - a small blood vessel runs in this ligament and along this infection may travel from the appendix to ovary.

The ovaries are attached to the broad ligament, and along this attachment (hilum) all blood vessels and nerves leave and enter the organ. The peritoneum stops abruptly at the attachment. The unattached border is convex. The upper or outer pole is broader than the lower, and comes in relation to the ovarian fimbriae of the tube. The lower pole it is/

is that is attached to the uterus at a point below and behind the juncture of the tube bythe ovarian ligament above referred to. The ovary is said normally to lie vertically with the free border backwards, (His). When fully formed, the ovary is a solid mass of vascular connective tissue stroma, containing vesicles ÷ Graafian follicles lined by epithelial cells, which enclose the ova. At its early developmental stage, this has a curious resemblance to a tubular, glandular structure: its epithelial cells being arranged in columns extending in from the surface, near which a lumen is sometimes seen. Eventually the cell columns (Pfluger's egg tubes) become separated into groups of cells which form the Graafian follicles.

The ovary, although an externally secreting gland, has not a direct communication with its duct - the Fallopian tube - which opens by a funnel-shaped opening into the peritoneal cavity, and leads into the uterus at its upper angle. The fimbriaeof the funnel catch the ova and by the action of cilia, which line the tube, the ova are conveyed to the uterus.

OVARIAN VESSELS.

The ovaries are directly supplied by the ovarian arteries, which arise in the abdomen from the front of the aorta, just below the renals. They pass down on the psoas muscle, and enter at the hilum between the layers of the broad ligament. There is a free anastomosis with the terminal branch of the uterine, and in many cases, this branch is so large, as to form the chief vascular supply of the ovary. Important, because it may explain the reason for degeneration of ovaries, which undoubtedly occurs, in some cases of hysterectomy, and thus harmonise the conflicting views held by such able observers as Zweifel & Abel, Mandel & Burger on the one hand, and Holzbach and Blair Bell and Marshall & Carmichael, on the other hand.

The ovarian artery sends numerous branches to the Fallopian tubes. The small branches, after entering at the hilum, pierce the proper coat, and run in sinuous lines through its substance. The veins correspond to the arteries, and form a plexus near the ovary, the Pampinniform plexus. The whole organ is exceptionally vascular.

The/

The lymphatics form networks round the large Graafian follicles, and communicate with those which accompany the blood vessels in their course through the stroma. They leave the ovary at the hilum, and join those coming from the ovary. There are said to be none in the corpora lutea, though this is not admitted by His.

The nerves of the ovary are derived from the ovarian plexus and from the uterine nerves, and send twigs along the tubes. The fibres are chiefly non-medullated, and are distributed to muscular tissue of the blood vessels of the ovary, and some parts to the cortical zone and ramify around the Graafian follicles.

PHYSIOLOGY of the OVARY.

The ovary, like many other structures in the body, - particularly glandular - has physiologically a dual function:-

(1) Oogenesis or egg formation, with the development of the Graafian follicles and ovulation, associated with which there is the subsequent fate of the erupted follicle which/

which fills with blood and then gradually absorbs or enlarges, dependent on whether the individual has been impregnated, when the follicle develops into the Corpora Lutea of pregnancy and continues to grow till about half way through the gestation period.

(2) The production of an internal secretion which influences the metabolism of the body generally, and has a specific action on the growth, nutrition and function of the uterus.

The development, maturity and decline of the reproductive function in a healthy woman, is spoken of, as the menstrual life. The beginning is termed puberty, and the cessation the menopause. It extends over a period of from 30 to 35 years. At puberty a person is said to be reproductively mature, but this is not strictly accurate, as cases of impregnation have occurred before menstruation, thus showing that ovulation and menstruation are not synchronous.

The first menstruation may be very abundant, but when established recurs every 28 or 30 days, and lasts/

lasts from two to seven days. There is a discharge of mucus and blood, venous-like blood, which does not coagulate, also debris and epithelium from the uterus and vagina.

Ovulation is the ripening and escape of the ova from the ovaries. When these do not develop, the individual is sterile and the characteristics of the child persist, the breasts remain small, pubic hair scanty &c. With the onset of puberty, the ovaries previously small and somewhat smooth on the surface, begin to enlarge and irregular projections form on the free surface, and they exhibit the periodic changes of ovulation. Ovulation is the growth and shedding of an ovum, which firstly sinks deeper down into the stroma of the ovary and then gradually approaches the free surface. The follicle, in which the ovary is, bursts, and the ovum is itself discharged, normally it passes into the Fallopian tube, and is propelled into the uterus, here should it become fertilised it grows into an embryo, - otherwise it passes out, probably with the menstrual flow. The ovum in any period being that shed at the previous and not at the corresponding ovulation.

It is readily understood when studied in the rabbit. The layer of short, clear columnar cells on/

on the surface of the ovary, germinal epithelium furnishes the primitive ova. These gradually sink down into the stroma, and become surrounded by a layer of cells which form a Graafian follicle. The stroma round the follicle becomes denser. On one side of the ovum, in the mass of cells, a cleavage is formed, and the space formed contains fluid. The ovarian follicle now resembles a signet ring, and the marginal cells are called the membrana granulosa, those round the ovum the discus proligerus. The follicle enlarges and approaches the surface of the ovary, the capsule becomes vascularised from the stroma. The follicle bulges on the surface, and the most prominent part which is non-vascular, ruptures, and the ovum, with the discus escapes, this equals the dehiscence of the ovum. The cavity of the follicle fills with blood clot, from the vessels in the capsule, and the capsule contracts in folds. The follicle convoluted walls with the blood clot is called the corpus luteum, because of the colour.

By degrees the liquid part of the blood is absorbed and the corpus luteum becomes paler and shrinks, and is converted into fibrous tissue and only a cicatrix remains on the surface of the ovary. This/

This being repeated causes the rugged and uneven surface in the adult ovary. When pregnancy occurs, the corpus luteum instead of reaching its full development in three weeks and atrophied in three months, persists in a well developed form for four months, then gradually diminishes, and only finally disappears three months after delivery.

There is apparently no constant relationship in the activity of the two ovaries, and the view that an ovum ripens at each menstruation, is now abandoned by most authorities.

HISTOLOGICAL STRUCTURE of the OVARY.

Cut surface shows two distinct parts:-

(1) That near the free surface the egg bearing part called Oopheron and

(2) That in relation to the mesometrium the Paroophoron which contains no follicles, but is very rich in blood vessels and nerves. To the naked eye, the follicles can be seen, and often more solid looking yellowish masses of varying size, these are the Corpora Lutea.

The follicles are embedded in a fibrous stroma, which has between its fibres many elongated cells/

cells, like those of embryonic fibrous tissue, also interstitial cells, which resemble those found in the testicle and Supra Renal. The stroma is more condensed at the surface and forms the tunica albuginea. At the hilum, where the blood vessels enter, the fibrous tissue contains plain muscle amongst its fibres. There is no true serous covering. Over the free surface, one sees a single layer of short, low columnar epithelium (germinal epithelium) among them some small and some larger epithelial cells, spheroidal = primitive ova. Here and there the epithelium is thickened, and dips down for a short distance, into the fibrous stroma of the ovary. These, in young animals, are in the form of long columns, and were first referred to by Pfluger (egg tubes). These columns become broken up into islets of germinal cells, by ingrowth of stroma, and from these islets the Graafian Follicles develop.

In all parts, except the hilum, one finds large numbers of spherical or ovoid vesicles, each with an ovum and mass of other cells, these are Graafian Follicles. They are of all sizes, varying from microscopic to size of a pea. The smallest contain only an immature ovum, with a single layer of/

of epithelium cells surrounding it. The largest have mature ovum surrounded by a considerable mass of cells - the discus proligerus which anchor it to the wall of the follicle, and the layer of cells round the wall = the membrana granulosa. The larger follicles contain fluid - the liquor folliculi. The epithelium lining the walls of the follicle develops into the epithelial tissue of the corpus luteum.

The smaller follicles are near to the surface, and in the child are very numerous, but many atrophy as growth progresses. The largest Graafian follicles are in the deeper part of the stroma, and it is only the enlarging from the fluid that again brings one part of the distended follicle to the surface.

The wall of the larger follicles is double with specially differentiated stroma as its outer layer, and a large granular celled layer as its inner, both layers contain blood vessels, the inner has a fine capillary network, the outer the arterioles and venules. The vessels enter the wall at its deepest part and converge towards its most projecting part (Stigma) where the rupture of the mature follicles takes place. The ova in the smaller follicles are of small size, but contain a larger, clear nucleus, and/

and large nucleolus, they have no distinct membrane. As the Graafian follicle enlarges, the ovum enlarges with it, and the follicular epithelial cells arrange themselves round the ovum, like a columnar epithelium. The membrane of the ovum now begins to appear, and is probably formed by the cells of the discus proligerus, but it does not wholly shut them off from the ovum for a connection with its cytoplasm is maintained by fine processes which pass through the membrane. These pores give the membrane a radial striation = Zona radiata. Inside the Zona, the ovum consists of cytoplasm or yolk granules, especially in the central part, and among them lies the nucleus, which has a prominent nucleolus, germinal spot. Mitotic division of the nucleus of the ovum usually goes on, after it is discharged from the Graafian follicles, and when it is in the Fallopian tube.
(Photographs Nos. 1-6.)

Before dealing with the symptoms of, and discussion of the menopause, the special points of emphasis regarding the histology of the ovary are :-

(1) The specialised epithelial germinal cells and follicles, and

(2) The peculiar interstitial cells of the stroma -

irregular/

irregular polyhedral cells - which Schäfer has pointed out resemble those found in the cortex of the Supra Renal and the Testicle, and which embryologically have a common origin from the Wolffian body.

These peculiar cells have probably a definite function, and considerable discussion has arisen, as to which of these specialised cells determine the metabolic changes, upon which are dependent, the menopausal symptoms, which arrive, when the ovary begins from age, atrophy or disease, to become functionless, or is ablated through surgical removal.

Probably up to puberty and after the menopause, the stroma cells are more important to the economy, than during the reproductive cycle.

NATURAL/

NATURAL & ARTIFICIAL MENOPAUSE.

Menstruation is a temporary and intermittent function which occurs in women, during the child bearing period of life, and is characterised by a discharge of blood mucus and epithelial debris from the genital canal. This is the outward and visible indication of an inward change. It is usually in abeyance during pregnancy, and in periods of ill health, but when it finally ceases naturally, usually between the age of 45 to 50. This time is spoken of as the natural menopause or climacteric. Menstruation, though often accompanied by the discharge of an ovum, is not necessarily so, and cannot be looked upon as being determined by ovulation, for the latter may occur before puberty, after the menopause and during lactation.

With the Menopause, the whole bodily economy is influenced, and, while the symptoms may be limited to the cessation of menses only, there is in most individuals a train of symptoms, so constantly present, as to be regarded as dependent upon, and associated with this particular period, and these may fall with greater or less severity on the various systems.

SYMPTOMATOLOGY/

SYMPTOMATOLOGY of the MENOPAUSE.

At this time various nervous symptoms are prone to develop, such as Vertigo, headache, flushes chills and neuralgias.

The digestive functions become upset, and one has this evidenced in the various dyspepsias, with capricious appetite &c. The circulatory system suffers, and attacks of syncope, palpitation, tacchycardia, with cold extremities are frequent.

Skin conditions as anaethesia, hyperaethesia, various eruptions, perspirations and pricking sensations are not uncommon, and hair grows more freely on the face.

Mental and emotional symptoms such as fear, melancholia, irritability of temper, loss of memory, together with change of disposition occur, and there is a special tendency to insomnia and epilepsy.

Cancer of the cervix and degeneration of myomata are frequent in their evidence at this period.

There is a disposition to put on fat, obesity being a common symptom.

At the same time there are structural changes in the uterus and tubes, &c. The uterus becomes/

becomes smaller, the walls are thinned and the glands disappear, - the epithelium atrophies. The tubes show similar atrophic changes. The ovaries become fibrotic and shrink; the vessels become hyaline and the follicles degenerate, and the germinal surface epithelium is lost, The vagina becomes narrowed, and its walls thin and atrophic. The labia lose their fat and shrink, till they are merely folds of skin.

Artificial or Surgical Menopause closely simulates the climacteric, and is probably, in each case, associated with, and in some way due to the withdrawal of the ovarian influence upon the body economy, and various theories are held, viz:- That it is due to the cessation of an internal secretion, which, with the atrophy of the ovary, is no longer present, and that the obesity, flushing, &c. develop in consequence.

This cannot wholly explain the condition, for we must remember, that the fact that ovulation may occur after the menopause, shows that the ovaries still functionate, and, on the other hand, menstruation occurs subsequent to double oophorectomy, in some cases. Again, the symptoms are looked upon as toxic, on the old theory that menstruation was a process by which the body got rid of a noxious product, and/

and as a highly specialised method of balancing anabolism and katabolism. The anabolic surplus being got rid of, but with the cessation of menstruation, these products accumulate and act as poisons.

The similarity of the symptoms of those produced in some disorders of the Thyroid gland, suggests the possibility of faulty Thyroid action.

In France, it is held that a substance Ovarin, derived from ovary, contains an oxidising ferment like spermin, and that various abnormal phenomena, during growth, as chlorosis and artificial menopause, are indications of auto-intoxication from products retained which normally are removed by the menses.

We know that many of the phenomena of the menopause can be readily controlled, relieved or abolished, by the exhibition of ovarian extracts, and in this connection, it is useful to note, that different observers have fixed upon special parts as being particularly therapeutically active, by some the corpora lutea alone are said to be beneficial, others use the whole gland. The interstitial cells are believed to have an important influence on development of adult characteristics.

Schäfer/

Schäfer has pointed out that these cells are polyhedral or irregular in shape, and lie in close relationship to blood vessels, and recall the structure of the cortical cells in the Supra Renal. Similarity is justified, for Miss Lane Claypon has shown that they have an embryologically common origin from the Wolffian Body, Sequira & Adams have shown that carcinoma of Supra Renals gave indications of sexual precocity.

The interstitial stroma cells have been held to be the important part of the ovary, and one concludes that the part or parts most efficient in controlling the symptoms must be the source of the internal secretion. It is probable that all the above parts are active, for it is now established that the stroma cells are potential corpora lutea, and that these together with the epithelial cells, lining the follicles, are all epiblastic in origin, being derived from the germinal epithelium, the more robust cells developing into ova, the lesser acting as supporting and food cells.

That metabolism is profoundly affected by the production of artificial menopause, has been experimentally proved by Loewy & Richter, (loc.cit.) who found an alteration in the gaseous exchange which

which indicated a 10% diminution of absorption of oxygen. There is also a diminished output of phosphorus. Thyroid administration, after double oophorectomy, causes an increase of oxygen to be taken up. It is concluded, therefore, that obesity results from the disturbance which takes place in the combustion of fats and other substances of a nitrogenous nature.

Thumin found that the ovarian feeding had no influence on the output of nitrogen in a patient with both ovaries removed.

Skrobansky found that the serum of guinea-pigs injected with ovarian extract, acted unfavourably on the ova of rabbits in situ.

To revert to the results of the exhibition of corpora lutea on the various symptoms of menopause, Jayle states that he found the vaso motor phenomena greatly benefited. De Cambulas states that the neurasthenic symptoms, such as insomnia and headache are relieved.

Lebreton finds that 0.05 grammes of dried corpora lutea twice daily, relieves the vomiting and nausea of pregnancy.

De Cambulas warns us as to the possibility of causing abortion, but Lebreton does not refer to this.

In/

In a recent case with excess of the above symptoms at the 2½ month, I exhibited one gramme per day of the corpora lutea for 10-14 days, with marked relief, and without the slightest indication of any tendency to abort. It is interesting in passing, to note that adrenalin chloride, and Thyroid Extract have each likewise, controlled these symptoms in my hands.

Saalfeld states, that the skin eruptions of the menopause, acne, eczema, prurigo, were favourably influenced by corpora lutea, and lastly Geissler states, that he has been able to relieve the anginal attacks with the same substance.

Thus, in turn, one sees that all the symptoms seem to be favourably influenced, and this is strongly suggestive, as well as almost a proof that the ovary furnishes a secretion, which having no excretory duct, is poured into the blood stream.

Further evidence of the ovary having an internal secretion is got from a study of the effects of removal of the ovaries. After ovariotomy, one gets with varying degrees, the symptoms of menopause, and beside the subjective phenomena, one is able to demonstrate structural changes in the other genital organs. These changes depend on whether the ovaries are removed during childhood, that is, before puberty, or later/

later in adult life. In the former case, the genital organs remain infantile in form and size, and the secondary sexual characteristics are not developed.

In animals, a castrated female is likely to take on the male external characteristics, this has been shown by several observers viz:- by F. Smith, who states, that young female cats castrated, acquire a head of the male type, with well marked jowl. Hunter described an abnormal ovary in a hen pheasant, which was correlated with the development of male plumage. In the barbarous parts of Asia, where young girls are castrated, such girls as adults do not develop sex characteristics, and often have resemblance to men. Poultry in old age sometimes present sex changes, hens and ducks developing the characteristics of cocks and drakes.

In women, the operation performed after puberty, when development has taken place, causes less marked results, than when done in early life. The most definite result is the cessation of the menses, though this is not invariably so, for at the present time, I personally have two cases, one a single woman, between 20 and 30, and the other a married woman between 40 and 50, each has had both ovaries removed in a most thorough fashion by experienced/

experienced operators, and each menstruates. After removal, there is a tendency to obesity and to atrophy of the breasts.

Most authorities agree, that the uterus undergoes atrophy, but some dissent from this statement, as expressing the direct result of the removal of ovarian influence, and ascribe it to the structural damage done to nerves, and the interference with the vascular supply of the uterus on the operation of removal of the ovaries. It is easy to see how this may be, for the vascular anastomosis is very marked between the ovary and uterus, and no matter what care is taken, these connections must, of necessity, be divided. These views are held by Buys & Vandervelte

In the work of Dr.F.H.A.Marshall on the results of ovariotomy in rabbits, special care was taken to avoid damage to the main vascular connections and his results gave evidence of degenerative changes in both uterus and tubes in all cases. The extent of the degenerative changes having a direct relationship to the time which had elapsed between removal of ovaries and the killing of the animal. The same observer, as controls, removed the uterus in young rabbits and young rats, and in no instance did he find any degeneration of the ovaries.

Bond records two experiments on the results of hysterectomy, and is essentially in agreement With Marshall/

Marshall, that no changes of a degenerative nature occur. He states, however, that the removal of Tubes and Uterus, by removing the source of the saline fluid, favours the overgrowth of luteal tissue in the ovary, and from changes which occurred in a transplanted ovary, on the supervention of pregnancy, viz:- overgrowth of luteal tissue, resembling a corpus luteum of pregnancy, he contends that there is also an internal secretion from the uterus, which acts on the luteal tissue of the ovary.

Despite these experimental observations, there are many clinical facts pointing to the dependence of the ovary on the presence of a healthy uterus, in order itself to function and remain healthy.

The persistence of menstruation can certainly be taken as indicating that the uterus is continuing to functionate after ovariotomy, and, therefore, that its functions depend largely on its own secretions. It is extremely unlikely, moreover, that a fibrotic uterus would menstruate. The explanation of this, is difficult. Abel & Zweifel, at the German Gynecological Congress 1899, traced the after histories of cases of hysterectomy, and found, that when the uterus was removed entire, the complete atrophy of both ovaries followed, with menopausal symptoms, similar to those of double oophorectomy. In cases of which a portion of the mucous membrane was left, menstruation/

menstruation persisted and menopause symptoms were absent.

Doran, in 1905, followed the after history of several cases of sub-total hysterectomy, and confirmed the opinion of Zweifel & Abel.

Bürger & Mandl, reporting on cases of hysterectomy in the human subject, both with and without the ovaries, states, that where the ovaries are left behind, they gradually atrophy and ovarian function ceases.

Holzbach states, that the ovaries do not atrophy after hysterectomy, unless the nervous connections are greatly interfered with.

Blair Bell holds a theory, that certainly seems to be supported by clinical facts : -

"That menstruation is due to a uterine secretion
"and the menopause due to its absence, and that
"this secretion circulating in the blood deter-
"mines ovulation, and that the ovaries invariab-
"ly atrophy, after removal of the uterus".

The theory of the internal secretions of the ovary he thinks inconclusive. Blair Bell has termed this Uterine Secretion - Uterin.

Heape has stated, that in his opinion oestrus is only possible, after the active changes in the/

the lining of the uterus which take place during the pro-oestrum, while Löwenthal appears to have held, that ovulation depended on a stimulus set up by the uterine changes in pro-oestrum. Whereas, the conclusions of Marshall & Carmichael definitely pointed to the fact, that in rabbits and rats, the uterus was dependent on the ovarian influence, and not the ovary on the uterus. Yet, in the human female, the evidence of the many observers quoted above, reverses this.

It is not logical to suppose, that in all cases one can expect analagous results in the very highly specialised organism of the human being, with such as occur in rabbits and rats, and herein must be recognised the limitations of all experimental work on lower animals, which can only be regarded as indicative of what may, and not what actually does occur in the higher species. May it not possibly be, that in the human subject after oophorectomy, the Thyroid (which is regarded as an additional sexual gland) takes the place of the ovary, so far as its internal secretion goes, in the maintenance of the bodily economy? Whereas, in the rabbit, the Thyroid is a much less important gland, it having been shown that its/

oblation does not produce any important changes. Its function being, in a measure, vicariously compensated for, by the extra colloid secretion of the posterior lobe of the pituitary, which, in the rabbit is large.

Herring showed, that granular bodies and hyaline material were more plentiful than usual in the posterior lobe and pars intermedia and masses of colloid were seen between the nervous elements.

Cecca and Zappi, showed that three months after castration, the changes noted in rabbits, were, a gain in weight, enlargement of the thyroid - the vesicles containing more colloid - the Supra-Renals showed increased medullary substance. No changes in the thymus or pituitary.

It would have been interesting to note here, whether in animals allowed to live twelve months after castration, the changes would not have been evident in the pituitary also, - which backs up, as it were, the thyroids and supra-renals; and in turn, the effect of removal of the pituitary on the thyroid-adrenals-and ovaries. The age of removal here, would be important.

The uterus, in the human subject, does not always/

always atrophy, whereas in the rabbit it does, after oophorectomy. This association of the Thyroid with the ovarian and uterine function, is supported by the fact of its evident enlargement at the menses, during pregnancy, and at the climacteric. That despite the conflicting views regarding the effects of Oophorectomy, there is ample evidence to show, that the ovary does furnish an internal secretion, and this is now generally admitted, and the results of the transplanting of ovaries - which, when the graft had taken in lower animals at any rate - have been effectual in preventing the degenerative changes which occurred in similar animals ungrafted. These grafts have apparently functioned as ovaries producing ova in some instances in rats.

The ability of the ovary to hypertrophy.

After removal of one ovary, the other rapidly increases in size. This has been looked upon by some as evidence of an internal secretion. I have found that in a few instances, after submitting rabbits to definite doses of X.Ray, and removal of one ovary, the other, did not show any compensatory hypertrophy. Similarly, in a rabbit, in which I removed the Thyroid and one ovary, the second ovary, six months later, actually showed considerable shrinkage. As a rule, however,/

however, on removal of one ovary, there is always a marked hypertrophy in the other, in which all the elements, stroma, follicles, etc., partake.

TRANSPLANTATION of OVARIES.

The grafting of ovaries in abnormal positions, has been attempted by many investigators, with varying degrees of success. It has been found that homoplastic grafts, that is, in the same individual, were oftener successful than heteroplastic grafts, that is, from one individual to another, in fact, most observers have failed entirely with the latter.

Ovarian transplantation has been tried by gynecologists and surgeons, and the reports in many instances are, that the grafts have been successful, few, if any, until recently, however, furnished any histological account of the state of the grafts, and if described, were not illustrated.

Limon, in 1904, illustrated microscopic sections of grafted ovaries, which do not seem to indicate very successful results.

In the human subject, several reports of cases are given in the literature, but in these, of course/

course, it is impossible to gauge the clinical results with the histological success of grafting, until examined post mortem. Cases are reported by Dudley (1897), Morris (1896) and Glass, (1899), in which women whose own ovaries had been removed had others grafted, and although these were reported as successful, no results of any subsequent examination of the grafted tissues were published.

An interesting case was reported by Morris (1906) in which after double oophorectomy, a woman had an ovary grafted, and four years later became pregnant, and gave birth to a child. Doran (1902) described a case of pregnancy, following double oophorectomy, in which no grafting was performed. A similar case was reported by Meredith (1904).

The explanation which naturally suggests itself, is, that a piece of the ovary had been left behind, and that from this, the ovum was shed. This was proved to be the explanation of menstruation recurring after the removal of both ovaries in a case reported by Pinard. If this was so in the other reported cases - which in the absence of post mortem evidence we are entitled to assume - then till now, no case of undoubted grafting of ovarian tissue successfully, is recorded in the human subject.

Cramer/

Cramer of Bonn has recorded a case, in which the ovary of a woman suffering from mollities was removed and transplanted into another woman, whose genital organs had shrunken and become atrophic. The atrophied genitals in the woman, in whom the ovary was grafted again became normal, the breasts enlarged and gave evidence of secretion, and the menstrual function returned. Cramer regards this as evidence that a grafted ovary can continue to function effectually.

Knauer seems to have been the first to record experimental grafting of ovaries in rabbits. He removed an ovary from a rabbit and transplanted it on to the uterine cornu of the same side of the same animal. After several months, he found the grafted ovary, which contained Graafian follicles - some healthy, but others degenerate.

In the following year Grigorieff records experiments on rabbits, in which the ovaries were removed from the normal position and grafted on the mesometrium, or between the layers of the abdominal wall, and found that they could be successfully planted on both muscle and peritoneum. He also records two cases of heroplastic grafts.

Ribbert records experiments on transplantation of ovaries, and found that during the first month/

month the peripheral part of the grafted ovary remained unaltered, but the central part became transformed into connective tissue. Later, however, follicles were again found in the central part. This, he attributes to increased nutrition, after the graft had got firmly fixed and acquired better vascular connections.

Halban found that, if in guineapigs at birth the ovaries were removed and transplanted under the skin, the other generative organs developed naturally.

Limon grafted ovaries in rabbits between the muscle layers of the abdominal wall, and on the peritoneum in same individual, and noted degenerative changes in the follicles, the interstitial cells after a time, acquired a perfect condition of vitality. The uterus did not atrophy after transplanting of ovaries to an abnormal position.

Carmichael records some success with homoplastic grafting of ovaries in rabbits, but furnishes no evidence that the grafts had any influence in preventing degeneration of the uterus.

Marshall & Jolly conducted a series of experiments on rats, in which they removed and transplanted/

transplanted the ovaries to abnormal positions, and noted the changes in the uterus.

In those animals in which the ovaries had been successfully transplanted, either on the peritoneum, or into the kidney, the uterus was found undegenerated. In those where the graft failed, degenerative changes were found. The observations were made at intervals of one to fourteen months. The successfully grafted ovaries exhibited all the characteristic histological features of normal ovarian tissue, excepting that the germinal epithelium was invariably absorbed. In some cases, only certain elements of the tissue could be recognised, after several months, the stroma might be normal, but the follicles had disappeared, or only luteal tissue might remain to indicate the site of the graft. In almost all cases, there was some degree of degeneration.

These observers found, that the successful grafts underwent the same cyclical changes as normal ovaries, showing follicles with ova and luteal tissue. In one case, a homoplastic graft was found healthy, after fourteen months, and a heteroplastic after six months, these being grafted into kidneys. Heteroplastic grafts were most successful when made from/

from one animal to another of the same litter.

The above experiments indicate that the influence of the ovarian substance is chemical, rather than nervous, as all nerve connections were severed, and that the uterus depends for nutrition, to some extent, upon substances secreted by the ovaries.

In the above Marshall & Jolly used rats, and have obtained healthy grafts, fourteen months after transplanting. In the rabbit, in the few experiments, in which, when enquiring as to the relation of the ovary to the saline secretion of the uterus, I transplanted ovaries to the peritoneum of the flank, in the same animal, I was unable to detect any ovarian tissue at the site, after eleven months. Probably, the bigger the animal, the less successful is one likely to be in transplanting organs, and hence it will be very interesting to have some definite information furnished in those cases of supposed successful grafting in the human subject, whose after histories have been carefully kept and followed up till the time of death.

THE/

THE ROLE of the OVARIES in MENSTRUATION.

The relationship of ovarian functions to menstruation has been frequently enquired into and various theories, as to the causative factors in menstruation advanced. In 1865, Pflüger advanced the theory, that menstruation was brought about by a nervous reflex, which arose from the pressure on the nerve endings in the ovary, by the growing Graafian follicles. Strassmann in 1895, supported the above, and reported that he had induced heat in dogs by increasing intra-ovarian pressure.

Elizabeth Winterhalter's alleged discovery of a ganglion in the ovary, tended to corroborate the above theory, but her observation has not been confirmed.

Goltz Pflüger showed that heat in animals is not due to a cerebral or spinal stimulus by experiments on bitches, in which he divided and removed the lumbar cord without interfering with the recurrence of prooestrum and oestrus. These are also facts which indicate that menstruation is not set up by a nervous reflex, due to ovulation or pressure of growing/

growing follicles. It has been pointed out, that in the human subject, ovulation and menstruation do not necessarily occur together. Heape has shown that in menstruating monkeys, the ovaries do not always contain follicles in a state of approaching maturity.

Although it is clear that menstruation and heat are not brought about by nervous influence, arising from the ovary, they are obviously dependent on ovarian influence of some kind, after double oophorectomy these processes usually cease. This is denied by some authors, and many cases of menstruation have been recorded, after removal of both ovaries by Doran, Blair-Bell, and others. Personally, I have at present two cases, which have been already referred to.

On the other hand, Morris gives an account of a woman, with an infantile uterus, who suffered from Amenorrhea, and who, two months after the transplanting of an ovary from another woman on to her fundus uteri, menstruated normally.

Glass describes a case of a woman, suffering from menopause troubles, after Oophorectomy, and in whom health was gradually restored and menstruation again occurred, after the transplantation of an ovary from another woman had been effected.

Cramer of Bonn, records a case of osteomalacia/

osteomalacia, in which the ovary was removed and replanted into another woman, whose genitals had atrophied, with the result that the genital organs became normal and menstruation started again.

The cases of atrophy of the uterus recorded after removal of the ovaries, also indicate that the menstrual and prooestral functions depend on the presence of ovarian tissue.

Veterinarians are agreed that heat does not occur in dogs whose ovaries have been removed.

Jolly & Marshall have shown that normal prooestrum followed by oestrus, can occur in dogs possessing only transplanted ovaries. This confirmed the observations of Knauer & Halban. In these experiments, the grafts seem to have survived long enough to exert some influence over the generative system, but on examination post mortem, they showed marked fibrous degeneration.

It may be concluded, probably, that the enhanced activity which the ovaries exhibit during the final stages of follicular development, is accompanied by metabolic changes, which cause an increased ovarian secretion, and on this secretion the function of menstruation chiefly depends. The distinct hypertrophy of the breasts, accompanied so frequently by pain and fullness, which occurs during the menstru-

al/

menstrual periods, is probably, due to an increase in ovarian activity.

In the course of my experiments, I frequently noted, that in rabbits, where one found the mammary tissue most plentiful, and the lacteal ducts large, in these cases also, the corpora lutea in the ovaries, were marked and well developed - suggesting a distinct correlation between luteal tissue and lactation: and, as usually lactation is accompanied by suppressed menstrual flow, the presence of luteal tissue, may have a corresponding inhibitory action, on the menstrual function of the uterus, although not actually being the cause.

There is a certain amount of direct evidence that menstruation is brought about by an internal secretion, produced by the ovaries. It has been shown, that the injection of ovarian extract causes a local congestion, and flushing with blood of both the internal and external genitals, which is also evident in the prooestrum and during oestrus normally.

Miss Lane Claypon and Starling used the ovaries of pregnant animals and described this condition, which one would expect to inhibit menstruation, although it determined a special flow of blood to the genitalia/

genitalia by a selective action.

Halban has furnished evidence that menstruation is due to the circulation of certain substances in the blood, but does not necessarily ascribe their origin to the ovary, as he has found the milk of suckling animals affected during the periods of heat.

Heape considers, that heat is due to a "generative ferment" circulating in the blood, but also that a specialised substance, developed periodically by the generative glands, which he calls "gonadin", is essential, and that the results of the combined action of this ferment and gonadin, is the production of the conditions of prooestrum and oestrus.

If we assume that the determining factor is one of ovarian activity, then for the purpose of practical application one must try to determine what part or parts of the gland are concerned.

Fraenkel has attributed the production of the secretion to the corpus luteum. He based this conclusion on several cases, in which the corpus luteum was destroyed by the cautery, and in these, the next menstrual period was missed. The theory, however, is disproved by the fact, that in most mammals ovulation does not occur until oestrus, or at any/

any rate, until the end of the prooestrum, and thus corpora lutea will not be present in the ovaries, as the corpora lutea from one oestrum, do not always persist till the next, which is usually several months after.

Heape observed the absence of corpora lutea in the ovaries of menstruating monkeys. Ries furnishes evidence, in the human subject, against this theory, and quotes a case of a woman, who menstruated normally, after an operation, in which an oozing corpora lutea was peeled out, for internal haemorrhage.

If the corpus luteum does not regulate menstruation, then one must conclude, that either the follicular epithelium, or the interstitial cells of the ovarian stroma are concerned in bringing about the process. General environment largely influences the recurrence of the oestrous cycle, as evidenced by the special feeding of domestic animals and it would appear, therefore, that the internal secretion is elaborated more freely by the surroundings, owing to increased metabolic activity of the ovary.

Further, one must not forget, that while it is most probable, that the prooestrous changes of the uterus are brought about by a specific excitant/

excitant, arising in the ovaries, no explanation has been given of the nervous upset that is present, and indicated by sexual feeling during oestrous.

THE CORPUS LUTEUM.

Numerous theories have been put forward to explain the formation and presence, as well as function of the corpus luteum. One view often expressed is, that its development is simply the outcome of the increased blood supply, which nourishes the entire genital tract during pregnancy. This is not an adequate explanation, and a little consideration shows, that at a time when the parts are most vascular as in the last stage of gestation, the corpus luteum is getting diminished in size. Again, the luteal cells most rapidly multiply, in the early stages of development; before that, there is no appreciable congestion of the genitalia. The corpus luteum has been considered as a sort of sponge, which developing, lessened the formation of scar tissue at the site of ovulation, thus preventing the circulation in the ovary being interfered with, in the cortical zone.

It was first considered in the light of a ductless/

ductless gland by Prenent. He thought it produced an internal secretion, which influenced general metabolism, after the manner of the ovarian internal secretion. He supposed that the corpus luteum had the further function of preventing ovulation during pregnancy or during anoestrus periods.

Regaud & Policard supported Prenant's theory, and reported having been able to detect droplets of a secretory substance in the cells.

Beard, independently suggested, that :- "the corpus luteum was a contrivance to suppress "ovulation during pregnancy, and that it shrivelled "before parturition to admit of ovulation recurring" but in many mammals, the breeding season recurs after an anoestrous period, often of some considerable duration, and that it is very unlikely that ovulation occurs during this period.

Sandes adopts Beard's theory, and states, that the corpus luteum disappears towards the end of lactation, when new follicles are beginning to grow and oestrous is approaching, and says that when it has formed the surrounding follicles, atrophy from increased pressure, from the rapid growth of the corpus luteum, or is due to the internal secretion, if there is one.

Marshall/

Marshall points out, that this seems a needless development of a structure, without it has a more important function, than to secure the degeneration of surplus ova, inside the ovary, instead of externally, and does not accord with the doctrine of utility and natural selection.

Born was the first to suggest the theory, that the corpus luteum formed an internal secretion, which assisted in the attachment of the embryo to the uterine mucosa, and Fraenkel experimented to test the accuracy of the theory. He removed the ovaries in a series of rabbits, at intervals, varying from one to six days after coition, the gestation period in the rabbit being 30 days. On killing the animals later, the embryos were found to have aborted or failed to become fixed. In other cases, the corpora lutea were described, as burnt out with the cautery without destroying the rest of the ovary, and these gave similar results. In controls, in which one ovary or only some of the corpora lutea were destroyed, the animals produced young.

Fraenkel backs up his theory, by referring to the histological structure of the corpus luteum, which he points out, is arranged like a ductless gland, being formed mainly of large epitheliod cells in/

in regular columns, and surrounded by a network of capillaries, not unlike the cortex of the adrenals. He says, that this only can account for its rapid growth, which is out of all proportion to the rest of the ovary: and, further, that when the corpus luteum is most hyperaemic, the rest of the ovary is anaemic, while at the end of pregnancy, when the blood supply is at its height, the corpus luteum is retrogressing.

Fraenkel lays stress on the origin of the luteal cells from the follicular epithelium, and not from connective tissue. All cases recorded of ovariotomy (double) during pregnancy, without abortion, were, so far as Fraenkel can ascertain, performed late in gestation. He holds that in non-placental mammals, the corpus luteum is rudimentary.

Sandes, who has carefully studied the formation of the corpus luteum in the marsupial cat, asserts, that there is a large corpus luteum. In monotremes, however, the formation is not normal, as although the follicular epithelium hypertrophies, there is no ingrowth of connective tissue or blood vessels from the follicular wall, which is the usual way of formation of the corpus luteum in mammals, as first described by Bischoff, and since corroborated by/

by several observers.

Fraenkel has pointed out, in support of his theory, that in ectopic pregnancy the uterus undergoes the usual changes of pregnancy, although there is no ovum in its cavity, and in normal pregnancy, these changes begin, before the ovum reaches the cavity of the uterus.

Pathological conditions of the embryo have been found associated with pathological ovarian conditions, e.g. Chorionepithelioma with lutein cysts. This association is held to support the theory of the corpus luteum being responsible for the attachment of the embryo in the early stages.

Marshall & Jolly, in a series of experiments on dogs, in which they performed double ovariotomy, at varying intervals, up to a month of gestation, found that the pregnancy discontinued in almost every case, excepting in fact one, where part of the ovary was found to have been left - thus corroborating Fraenkel's view.

In several instances in rabbits, after the 9th day, I found that double ovariotomy did not interrupt the pregnancy, but that earlier they invariably aborted, and were very prone to do so, after the 22nd day.

Fraenkel's/

Fraenkel's general conclusions, as to the function of the corpus luteum are that:-

It is a ductless gland which in the human female is renewed every four weeks during reproductive life. Strictly speaking, there is only one corpus luteum, which is regenerated periodically in different positions in the ovary. Its function is to control and raise the nutrition of the uterus from puberty to menopause, thus preventing its atrophy, and also to prepare the mucous membrane for the reception of the ovum. If the ovum becomes fertilised, the corpus luteum is responsible for maintaining the raised nutrition, during the first part of gestation. If the ovum be unfertilised, then it only produces the congestion and hyperaemia of menstruation and degenerates, until it is renewed in a fresh position. Since the corpus luteum is, to all intents and purposes, the ovarian gland, then extracts of it and not of the entire ovary should be used therapeutically.

Observations and facts tend to confirm the part of the theory which assigns the function of governing the fixation of the ovum and helping to maintain its nutrition, during the early part of pregnanby. The extended theory, however, is not tenable, as it has been shown, that in many animals, heat, and probably/

probably, therefore, ovulation occur at infrequent intervals, and in some animals, at any rate, ovulation does not take place until oestrus, so that at the time of prooestrum (menstruation) there are really no corpora lutea present in the ovary.

Again, there are no grounds from the evidence of the experiments of either Fraenkel or Marshall & Jolly, for asserting that the corpus luteum governs the fixation of the embryo, other than in the indirect sense of stimulating the mucous lining of the uterus by its secretion, to undergo the necessary hypertrophy for embedding an ovum. In this sense, also, the luteal secretion nourishes the embryo, by raising the nutrition of the uterus. Since in the latter part of pregnancy, the corpora lutea degenerate, it is not unlikely that the fibrotic changes in the decidua serotina, in the latter part of gestation, are directly correlated with the degeneration of the corpus luteum.

It is recorded by Essen-Möller, and by Flatau, that pregnancy in women was not interrupted by double oophorectomy in the early period of gestation. This may, possibly, be explained, by a small portion of an ovary being left behind, accidentally, at operation.

Daels/

Daels records, that in guineapigs, double castration invariably caused abortion, during rather more than the first half of gestation.

Ancel & Bouin hold, that there is a close parallelism between the growth and regression of the corpus luteum, and a series of cyclic uterine changes.

In the rabbit, there is said to be a close relationship between the development of the corpus luteum, and the growth of the mammary gland. I have noted in those rabbits, with good secretion of milk, and large lacteals, the corpora lutea were also well developed.

Regaud & Dubreuil question whether the corpus luteum has any influence on the non-gravid uterus.

Loeb has been able, by damaging the mucous membrane in guineapigs, to produce deciduomata, the nodules develop through a proliferation of the inter-glandular connective tissue, and that this occurs most readily, between the fourth and eighth day, after copulation or heat, which would correspond to the period of formation of fresh corpora lutea in the ovaries. In the absence of the ovaries, deciduomata could not be produced. Transplanted pieces of the uterus in the subcutaneous tissue developed deciduomata. It is held, therefore, that at certain times, after ovulation, the ovaries and probably the corpora/

corpora lutea, elaborate a special substance in the presence of which trauma may produce deciduomata.

After the removal of the ovaries, the uterine mucosa atrophies, and it is unlikely, that this process can be arrested or prevented by the presence of a fertilised ovum, in the early stages of pregnancy. An ovum is on the other hand, not likely to find an attachment to degenerated tissues. After the great hypertrophy and enlargement of the later half of pregnancy, which takes place in the uterus, and because of the then greatly increased vascular supply, it would seem that the ovaries can be done without, though it is difficult to prove that the after development is exactly normal after double oophorectomy. The interstitial cells of the ovarian stroma, have been shown to increase during pregnancy, but not to the same extent as the luteal cells; and they may, consequently, also produce an internal secretion. This is more than likely, for Miss Lane Claypon has shown, that the interstitial cells are derived from the same source as the ova and follicular epithelial cells. Mechanical pressure has been suggested as inhibiting the growth of the stroma cells, and so preventing their hypertrophying to the same degree, as the luteal cells.

While mechanical pressure may inhibit the increase/

increase of the stroma cells, it is also likely that the stimulus set up at the site of the trophoblast, will act more directly on the epithelial cells of the follicle, as being the cells more advanced in the life history, than the stroma cells, and hence more ready to proliferate, and the stimulus probably, next tells back on the germinal epithelial cells, but to a less extent than on the stroma cells, so that really what happens is, hypertrophy and proliferation of all the elements, the epithelial cells of the follicles, that is the luteal cells in a greater degree, the stroma cells less so, and germinal epithelium least of all.

The regressive stage of the corpus luteum may be determined by its own secretion, which, after reaching a certain height, may act inimically on the cells producing it, as is seen in the lowest forms of life, e.g. the yeast plant, which by its own product kills off itself.

Therapeutically, the ovarian extract has been used, both as a product of the whole gland, and as a dessicated powder of the corpus luteum, the latter seems to be the more efficient clinically.

Obesity, and almost all the various phenomena referable to the menopause, viz:- headache, flushings/

flushings, tremors, parasthesias and neurasthenia, as well as the skin disorders, have all been favourably influenced by the exhibition of corpora lutea grs.V. dried, three times a day.

In the excessive nausea and palpitation, which occurs in some cases of pregnancy, relief has attended its administration.

Personally, I have used it to arrest the excessive haemorrhage and loss which occurred in a case at the climacteric, the discharge was checked after the administration of 60 grains of the dried corpora lutea. It is also indicated in deficient secretion of milk, and in a patient (primapara) who menstruated, during lactation, I found that corpora lutea improved the quantity and quality of the milk.

It has, apparently, no blood pressure raising effects, but seems rather to have a selective, specialised effect on the secreting tissues of the mammary gland. This has been thoroughly investigated by Schäfer and Mackenzie.

THE/

THE SECRETIONS of the UTERUS & CERVIX.

T H E U T E R U S .

STRUCTURE.

HISTOLOGY.

This organ consists of the body or main part, the fundus, that which lies above the entrance of the Fallopian tubes and cervix or lower part, which, by the Os uteri, opens into the vagina. Its walls consist of three layers, outer serous, inner mucous and intermediate or muscular.

The outer serous layer is really simply an investment of peritoneum. The Muscular, the thick part of the wall of the uterus, is composed of plain muscular fibres, of small size and short in the non-gravid uterus, they lengthen greatly in pregnancy. The fibres interlace, and are arranged in layers, with areolar tissue throughout, containing a large number of blood vessels and lymphatics and some nerves. The areolar tissue is more abundant near the outer surface. There are three layers, the outer two corresponding/

corresponding to the two usual layers found in other muscular organs, the innermost being a specialised and greatly hypertrophied muscularis mucosa.

The outer layer of muscle fibre, forms a continuous but thin sheet, beneath the serous, and has incomplete bands situated more deeply. The greater proportion of these fibres begin in the cervix and arch up over the fundus and body obliquely, and are continued on, into the Fallopian tubes on either side, and out into the broad ligaments and some into the round ligaments and end in the groin. While from the posterior and anterior, strong transverse bands pass out into the ovarian ligaments: other fibres again run back from the cervix beneath the utero-sacral folds.

The inner layer of the muscular coat is seen chiefly on the back of the uterus. It is thin, and the fibres stretch over the fundus and towards the sides, and run irregularly between the blood vessels. It is not easy to determine exactly, the limits of this layer, as there is no distinct submucous areolar tissue, as a distinct coat, as in most hollow viscera, but the line of the distribution of the blood vessels, serves to distinguish the plane of division between the muscular layer proper and that of the mucosa. (Photograph No.7.)

THE MUCOUS MEMBRANE.

This coat is characterised by the enormous hypertrophy of the muscularis mucosa, above mentioned, and this forms the greater part of the whole uterine wall. The presence of this mass of muscular tissue, in the deep part of the mucous membrane, is shown in section, as a distinct part and differentiated from the inner part of corium. It consists of bands of fibres, arranged regularly, near the fundus, and in many concentric rings, round the openings of the tube, lower down the fibres run more distinctly transversely and from the so called os internum and os externum sphincters.

In the neck of the womb, there are longitudinal fibres inside these.

In a microscopic study of the uterine wall one gets an excellent definition of the arrangement of the fibres of the muscular coat proper, and also of the muscularis mucosa, in sections, from the uterine cornu in the rabbit. Here the distinct differentiation between the corium, with its stroma, and tubular glands and the transversely running fibres of the muscularis and outside this the areolar tissue, carrying/

carrying the blood vessels with the muscular coats proper outside again, and most externally the serous coat are all clearly seen.

The mucous membrane of the lining of the body cavity, differs considerably from that of the cervical lining. The mucous membrane of the body is smooth, except during the menstrual flow, and in the unimpregnated state, is devoid of ridges. It is very soft and velvety, with a sponge-like feel, and is very vascular and dull red in colour.

Microscopically, the membrane is usually described as consisting of peculiarly undifferentiated connective tissue, rounded or spindle-shaped cells embedded in a homogeneous ground substance, with fibrils, which form a meshwork, containing lymph spaces. There is a rich capillary network near the surface, but the whole thickness of the membrane is very vascular. The inner surface is lined with a single layer of ciliated, columnar epithelium, on which opens the mouths of the uterine glands. They are simply dippings down of the lining and form tubular glands, they become convoluted at the deeper parts, and end blindly among the bundles of the muscularis mucosa, the lowest part of the glands is sometimes filled with cells. Nerve fibrils have been/

been traced into the epithelial lining cells, which may be low cubicle and without cilia.

The mucous membrane of the cervix is firmer, and less spongy than that of the body. It is thrown into rugae, forming the arbor vitae, and between the rugae, there are many tubular and saccular invaginations, forming larger glands, than those of the body. In the lower part of the cervix, the mucous membrane is formed of stratified epithelium, with many vascular papillae, but in the upper half, the epithelium is ciliated epithelium. The glands of the cervix are short, with a large lumen. They are always lined with ciliated columnar epithelium. Besides these, almost always, many ovula Nabothi are seen, these are clear yellowish vesicles, which can be seen to the naked eye, the exact nature of these is doubtful. In the gravid state, the glands of the cervix, secrete a quantity of thick tenacious mucus, which plugs the cervical canal, the blood vessels have thickish walls. The Os Uteri is covered internally, in its lowest part, with stratified epithelium, and like the vaginal portion, it is vascular, but has no glands. The blood vessels of the uterus, come from the right and left ovarian and uterine. They anastamose freely, and are very tortuous. After passing a short distance into the uterine wall, they divide, and penetrate the muscular tissue of/

of the mucous membrane, supplying it with capillaries. They then pass towards the inner portion of the membrane, and open into a network of large capillaries, which pervades the tissue round about, especially round the glands.

In the cervix, the thick walled vessels, after entering the mucous membrane, divide into very small branches, which pass directly towards the surface and open into the capillary network there, and from this network, loops pass into the papillae. The veins correspond to the arteries, they are large with thin walls, and form sinuses in immediate relationship with the stroma of the mucous membrane.

The lymphatics begin in the mucous membrane, as cleft-life spaces, there are also well marked lymphatics, extending as a plexus, throughout the membrane. They open into plexuses in the muscularias mucosae, and muscular coat proper, and these again, into vessels in the serous coat.

The nerves of the uterus are both medullated and non-medullated, and in the lower animals, small ganglia have been observed on the non-medullated. The nerves are derived from the Inferior Hypogastric and Spermatic plexuses and also from the 3rd and 4th Sacral.

SECRETIONS/

SECRETIONS of the UTERUS & CERVIX.

That there is an external saline secretion has been already demonstrated and the conditions under which it is secreted, and its function, are fully dealt with later on, in recording the experiments done. Very little at all is known of the internal secretions of the uterus and cervix. Some surgeons and gynecologists have adopted the view that the uterus is capable of functional activity, independently of the ovaries, although the bulk of clinical evidence indicates that the uterus ceases to functionate, after removal of the ovaries. It is held further, by a few, that instead of the above, it is likely, that the uterus possesses independent power of activity, and in fact, by its secretion, regulates and stimulates the function of the ovaries. The substance elaborated, has been termed uterine.

In recording the after histories of hysterectomy, Zweifel & Abel stated, that when the whole uterus was removed entire, atrophy of the ovaries always followed, and menopausal symptoms ensued, similar to those occurring after ovariotomy. In those cases/

cases, however, where a portion of the uterine mucous membrane was conserved, menstruation continued, and there were no menopausal symptoms.

Doran, reviewing 60 cases of subtotal hysterectomy, supports Zweifel & Abel, and attributes to the small portion of the uterine mucous membrane which is left, the power to maintain menstruation.

Mandl & Burger in 1904, expressed the belief that when the uterus was removed, and the ovaries conserved, there is a gradual cessation of function on the part of these organs, as the result of degeneration.

Holzbach contends, that the ovaries do not usually degenerate after hysterectomy, except in such cases, as the nervous connections are interfered with at the operation.

Blair Bell thinks from his investigations that menstruation is brought about by an internal secretion of the uterus, and that ovulation depends on the circulation of this secretion, which he calls "Uterine".

Bond has advanced the view, that the saline secretion of the lining of the uterus, influences ovarian secretion, and that the nature of the influence is one of antagonism, so that the withdrawal of the/

the saline secretion by hysterectomy, favours the hypertrophy of the ovaries. This view is directly opposed to Blair Bell's, for, he attributes ovulation and hypertrophy of the ovary as due to the circulating of the secretion of the uterus.

Bond records two experiments on the results of hysterectomy in rabbits. In one after total hysterectomy the ovaries were normal five months later. In the other only one cornu was removed and five months later, the ovaries showed no degeneration. From these, he asserts, that the prevention of the saline secretion of the mucous membrane of the uterus favours the overgrowth of luteal tissue in the ovary.

Importance has been attached to the established fact that if pregnancy supervenes after ovulation, then the corpora lutea of the ovary continue to grow for a considerable time, but in the absence of pregnancy, this growth of the corpora lutea soon ceases and does not, by any means reach the same extent of hypertrophy, suggesting that the uterine hypertrophy and growth, particularly of the mucous membrane at the site of the ovum (bed) is associated with the production of a secretion which influences the ovaries and excites the growth of luteal tissue.

Bond/

Bond suggests that this substance is directly antagonistic to the saline secretion of the anoestrous uterus.

Other authors have suggested theories which indicate a dependence of the ovaries upon some function of the uterus. (Loewenthal). But, apart from the experiments of Bond (2) and those of Marshall & Carmichael, no investigation on the effects of experimental hysterectomy has been made. The last observers removed the uterus from several immature rabbits, and killed the animals when fully grown and record that in every experiment the ovaries had developed normally, and in those in which copulation had taken place, typical corpora lutea were present. In no instance in Marshall & Carmichael's series, was there any evidence of ovarian atrophy, and they conclude that the growth and development of the ovaries is in no way dependent on the presence of the uterus. This conclusion, though arrived at, after painstaking work, and apparently from the records, justifiable in rabbits and rats, is directly opposed to the contention of Blair Bell, before referred to, who supposes ovulation to depend on the circulation of a uterine internal secretion, and to the clinical observations of Zweifel & Abel, who attribute the source of this uterine secretion to the mucous lining, and declare/

declare that atrophy of the ovaries always follows the entire removal of the uterus.

Mandl & Bürger, in a very exhaustive record of the subsequent histories of cases of hysterectomy, where the ovaries are left behind, state, that there is a gradual cessation of ovarian influence. It is somewhat difficult to explain and harmonise this entire want of accord of experimental results, with the clinical facts and evidence recorded by the above observers, and such surgeons as Doran and Pozzi. The explanation which suggests itself, is, to some extent, anatomical. The vascular interference in operation, on the human subject, is greater, and often more direct than in rabbits, for the main vascular supply of the ovary, in the human subject, is frequently by the anastamotic branches from the uterine vessels. Whereas, in the rabbit, it is possible to remove the uterus, with very little disturbance of the vascular supply of the ovaries. Moreover, hysterectomy in the human female, is always performed for pathological reasons (and where there are symptoms of hemorrhage) the uterus thus being often very vascular. It is conceivable, therefore, that with the removal of the organ, and consequent severing of the/

the enlarged vessels of supply, thus cutting off the increased vascular content of the pelvis, will reflexly diminish the supply available for the ovaries, which, for the time, have had an extra amount of blood, during the pelvic congestion, caused by the pathological condition in the uterus, with the withdrawal of the extra supply, there is consequent atrophy of the ovaries and cessation of function. This, at any rate, accords with clinical observations. The conditions of experimental hysterectomy, in the rabbit, are entirely different, for we are dealing with a normal blood supply, and without the same degree of anastamosis, and common source of blood supply between the uterus and ovaries.

I have recorded later, the results of my own experiments in rabbits, in which, after hysterectomy, two were treated with extract of the anoestrous uterus, and the condition of the ovaries compared with others of the same age, which were not subsequently treated.

The series of cyclical changes undergone by the ovaries, are all closely correlated with those which take place in the uterus. The growth of the follicular epithelium and interstitial cells of the ovary, at the outset of pregnancy, is simultaneous with the hypertrophy of the uterine mucosa and wall, and/

and it seems to me only reasonable that both are explanable on the increased vascularity of the uterus, which ensues at pregnancy, in turn causing increased function on the part of the uterine mucosa, whereby more uterine secretion "Uterin" is thrown into the blood, and stimulates the ovary, and there is growth of luteal tissue which continues until the size of the ovum is such(that is in the latter months of gestation) that it requires all the "Uterin" womb milk produced for its further development, thus deprived, the corpus luteum gradually involutes and degenerates.

The very close co-ordination between the uterine and ovarian functions is thus clearly shown, and Starling has suggested, that this is due not to the production of any chemical substances acting as specific internal secretions, but to the development of a specific sensibility, on the part of functionally related tissues. While this is possible, still the definite character of the cyclical changes in the uterus and ovary, points rather to the conclusion that there is a special secretory function.

SECRETIONS of the FALLOPIAN TUBES, VAGINA &C.

There is no evidence that any internal secretion/

secretion is produced by the Fallopian Tubes.

The mucous lining of the tubes is constantly bathed by a saline secretion which is made evident on ligation of the tubes and produces a hydro-salpinx. This external secretion is referred to later.

HISTOLOGY of the TUBES.

If one regards the ovary as a gland which produces ova, the tube may be looked upon as its duct. It, however, is different from other gland ducts, in that it has no direct communication with the gland, but opens into the peritoneal cavity near that organ, by a minute opening in the centre of its fimbriated extremity. The fimbriae come into very close relationship with the ovary and one is attached to its upper pole. When the ovum is discharged, it falls most often on one of the fimbriae, and the cilla which are in constant motion, cause a current towards the tube, and the ovum is drawn into the orifice and passes along the tube to the uterus, which may be regarded as the fusion of the two tubes. The uterine end of the tube opens into the uterine cavity, at its upper angle, by a very small aperture, but in most of its course/

course, the lumen is much larger.

STRUCTURE of the TUBE WALL.

The three coats are distinct:-

1. The outer serous covering derived from the peritoneum which invests it, except where attached to the broad ligament.
2. Two muscular coats, inner circular and outer longitudinal, which are layers of plain muscle fibres.
3. A mucous coat, which is thick and thrown into permanent folds.

These are no glands in the mucous membrane and only a few elastic fibres. The tube is lined throughout its whole length, with ciliated epithelium. At its open fimbriated end, the ciliated epithelium is in direct relationship to the serous peritoneal coat.

The blood vessels and nerves pass on to the tube wall in a layer of loose areolar tissue, beneath the serous coat.

The muscle coat is strongest at the uterine end, to help the more effectually to shut off the distended/

distended uterus when gravid. The mucous coat is best developed and thickest at the fimbriated end to catch the expelled ova and waft them towards the uterus. (Photograph No.8.)

Ballantyne (J.W.) has described a further thin layer of longitudinal fibres inside the circular, but there is no definite line of division between the muscular coat and the mucous membrane, and probably most of this is to be regarded as hypertrophied muscularis mucosa.

The folds or plicae of the mucous membrane have secondary folds on them in the ampullary part. The deep furrows, probably represent glands which otherwise are unrepresented, as this increased extent of mucous surface suggests a secretive function of the mucous membrane. Although the lining of the inside of the tube is termed mucous membrane, it is found that its secretion contains no mucous and very little protein.

THE BLOOD VESSELS, LYMPHATICS And NERVES of THE TUBES.

The arteries are derived from the upper terminal branch of the uterine and the anastomotic from the internal ovarian. The veins run to connect with/

with the ovarian and uterine and form a plexus along the line of the broad ligament.

Efferent lymph vessels pass to glands in front of the Vena Cava and Aorta. Both the lymph and blood are distributed freely to the mucous membrane, and the muscular layers have each a special capillary plexus.

The nerves come from fibres which go to the uterus and ovary and are distributed to the muscle and mucous coats.

The external secretion of the saline fluid which bathes the mucous lining, and which is similar to the fluid, which accumulates in a hydrosalpinx, is the product of the mucous membrane and is probably protective to the ova and furnishes a fluid current owing to the action of the cilia and which carries the ova towards the womb, and what is equally as important, serves as a preventive against ascending infection from the uterus and vagina.

ANATOMY/

A N A T O M Y .

THE VAGINA AND ITS SECRETIONS.

The vaginal wall is composed of a thick outside fibrous wall, an intermediate muscular and inside mucous. The wall is thickest anteriorly, where the urethra is embedded. It is firmly fixed to the neck of the bladder, but posteriorly, and laterally, the tissue round about is looser and areolar in character and allows of more play and distension. At the upper part posteriorly, for about a quarter of its length, the peritoneum comes into relation with it, and forms a cul de sac - Recto Vaginal fossa - outside the vagina particularly near the entrance is a layer of erectile tissue.

The muscular walls are composed of unstriped fibres, not in definitely separable strata, but chiefly running longitudinally and continuous above with those of the uterus.

At its vulval end, it is embraced by circular fibres (Sphincter). On the inner surface of the vagina anteriorly and posteriorly, we find a thickened/

thickened ridge, elevated into the columns of the vagina, also transverse folds, these are well marked in the virgin, but less so after coitus and disappear after parturition. Besides these rugae on the mucous membrane, there are vascular microscopic papillae projecting into a stratified scaly epithelium - but the papillae are low and sparse. It is said that the vagina is unprovided with glands and that its secretions are derived from the uterus.

The orifice and vulva are kept moist by the secretion of Bartolini's glands, and many other minute glands on the inner aspect of the labia.

VESSELS & NERVES.

The vagina is richly supplied by vessels and nerves. The arteries are the vaginal - internal pudic, uterine and vesical. The veins correspond but they first surround the vagina and form a plexus on either side - vaginal plexus.

There is a close network of lymphatics in the mucous membrane which also contains a considerable amount of lymphoid tissue collected into nodules.

The/

The nerves are derived from the hypogastric plexus of the sympathetic, from the fourth sacral and pudic nerves; they can be traced to the erectile tissue - muscle fibres, and on to the epithelium.

THE SECRETIONS of the VAGINA.

The vagina being unprovided with glands its secretions are, most probably, derived from the uterus and cervix. The secretion normally is acid and said to be due to the vaginal bacillus, which produces a secretion, containing lactic acid and in a healthy individual, acts as a protective against all bacteria. The ordinary pathogenic bacteria are rendered harmless by the vaginal bacillus.

The whitish secretion of the vagina is derived from the mucous glands of the cervix and from the endometrium. In the pregnant state, the secretion is more abundant and often curdy in appearance. During pregnancy, this secretion is of great physiological importance, and its bacteriological characters have been carefully studied. In a healthy pregnant woman, it is abundant, and occurs as a whitish-flaky-semi-solid material, not unlike the smegma secretion in/

in appearance: it is acid, which is due, as stated above, to the vaginal bacillus. The secretion is frequently different from this being thinner, more yellowish and less definitely acid in reaction. This variety of secretion classed by Döderlein as "abnormal", may contain various species of micro-organisms, but probably none are pathogenic, except in cases of local disease. The normal acid secretion possesses definite bactericidal properties, for streptococci, introduced into the vagina experimentally, are all destroyed by it, in from twenty-four to forty-eight hours; and this property is attributed to the direct action of the vaginal bacillus. Whether the secretion can destroy all kinds of pathogenic organisms, we do not, as yet, have definite evidence - enough, however, has been proved experimentally, to show that the vaginal secretion of a healthy pregnant woman forms a natural protective barrier against the invasion of the genital canal, by micro-organisms coming in from without.

That the vagina has a secretion which is not derived from either the cervical or Bartholinian glands is proved by the following considerations:

The cervical canal normally is shut off from the vagina/

vagina by a tenacious plug of mucous: the Bartholinian glands, on the other hand, open outside the vagina on the outside of the hymen, and they secrete very little fluid, and again in closed cysts of the vagina, a typical vaginal secretion is found, which differs markedly from the cervical secretion.

The vaginal secretion is due to the exudation of some lymph-serum, together with the shedding of squamous epithelium. It forms a thin coating on the surface of the vagina, and is normally a thin opalescent fluid, but as stated above, when abundant it forms a white flocculent curdy material. The reaction is strongly acid, being equivalent to 0·4% sulphuric acid of 0·9 lactic acid. The acidity disappears during pregnancy, a few weeks after menstruation and for six weeks to twelve months after labour. In the new born, the reaction is neutral, feebly acid or alkaline in pathological conditions and strongly acid during pregnancy.

MICROSCOPICALLY examined the secretion in the infant contains only epithelium, - in the virgin and in normal pregnancy, one finds in addition the vaginal bacillus, which occurs in the form of short, straight rods, and is anaerobic and grows at body temperature/

temperature on agar, or in bouillon-blood serum or milk. In pure cultivation, it produces lactic acid, equivalent to 0·5% sulphuric acid.

ROLE of the VAGINA BACILLUS.

To this the presence of lactic acid is due for when absent, the reaction is always neutral, and the bacillus inhibits, and before long, kills pathogenic micrococci, when the vagina bacillus is absent, both saprophytes and staphylococci flourish.

The Monilla Candida is a fungus which is harmless and can only be grown in the presence of the vagina bacillus.

As a result of the protective influence of the vagina-bacillus, it happens, that when pathogenic organisms are found in the normal vaginal secretion, they are always in an attenuated condition and of a weakened virulence.

EXPERIMENTAL/

EXPERIMENTAL WORK.

EXPERIMENT I.

TO COLLECT AND EXAMINE THE SECRETION OF THE LINING of the TUBES and ENDOMETRIUM.

A WHITE FRENCH RABBIT full grown, weighing 2 Kilos.150 grammes, was anaesthetised, and the abdomen opened with aseptic precautions. The right and left uterine cornua were doubly ligated with silk, - thus isolating the two portions. Abdomen was closed and union aseptic. Ten days later a swelling was detectable in the region of the right cornu, the vagina was moist, and the rabbit healthy and well. Two months after the ligation of the cornua, the animal was killed, weight 2 Kilos 40 Grms. Examination showed greatly distended left cornu (Hydrometra) and contained 3 to 3½ cc.'s of a pale watery, slightly opalescent fluid. The right cornu was also distended and thickened, but to a less extent than the left.

MICROSCOPICALLY the fluid contained cellular elements/

elements and some granular leucocytes. (Photograph No. 9.).

CHEMICAL EXAMINATION of the fluid for nitrogen, to determine whether of the nature of exudate or transudate, shows it to contain very little protein, only 0·72%, actually 1·2 mgs. of nitrogen per cc. & also contains a considerable quantity of sodium chloride, and a little phosphate of calcium and some serum albumin. It is thus, probably of the nature of a transudate from the lining endometrium. This animal was not pregnant.

EXAMINATION of CORNU. In the right cornu, on section to the naked eye, the walls were only slightly stretched. The left cornu walls were considerably dilated and thinned.

The whole cornual wall is markedly thinned out, especially the mucous layer. The epithelial lining of the mucous layer consists of columnar cells whose size has become distinctly increased. The connective tissue of the mucous membrane has been extremely reduced, and consists merely of the core of the small papillary projections which rest directly on the muscle coat.

MICROSCOPICALLY the muscle bundles of the cornua are opened out, the fibres are distinctly enlarged - their/

their appearance would seem to denote hypertrophic change - the neclei take the stain well. This hypertrophy has evidently been an attempt to resist the enlargement.

RIGHT OVARY weight 0·095 grms. shows numerous primodrial follicles and ripe ova, and a small amount of fibrous tissue in stroma. The Graafian follicles with the ova are well seen.

LEFT OVARY weight 0·112 grms. also shews several follicles and ova, but fewer than in right and greater amount of fibrous tissue.

The follicles suggest atresia in some places - the ovum being shown shrivelled, with irregular outline, and the cells extending in from the lining of the follicles. Atretic follicles occur in the rabbit, as in oestrus unless coitus takes place there is no ovulation.

(Photographs Nos.9,10,11,12)

EXPERIMENT/

EXPERIMENT IA.

IS THIS SECRETION DUE to the ENDOMETRIUM and INDEPENDENT of the NERVOUS CONNECTIONS of the CORNU? IF SO IT SHOULD OCCUR IN TRANSPLANTED PIECES of the CORNU.

December 22nd.

A BROWN RABBIT, weight 2 Kilos.100 grms. was anaesthetised and prepared. Abdomen opened in mid-line, and the right uterine cornu doubly ligated with silk. The piece between the ligatures 1½" in length, was isolated and transplanted in the right flank, under the peritoneum. The abdomen was closed and the animal made a good recovery - healing was aseptic.

Three weeks later.-

Rabbit in good health. Vagina congested and suggested Oestrus. Suspicion of swelling in right flank, in region of transplanted cornu.

On January 22nd -

A month after transplantation and ligation of cornu, the rabbit being in good health, was anaesthetised and killed, and the abdomen was opened. In right iliac region the right cornu between ligatures was/

was greatly dilated with clear fluid, and the walls thinned. The isolated piece was healthy, had grafted and was dilated. The distended cornu contained 3·75 cc. of clear opalescent fluid. The fluid was stained and examined, and showed many granular leucocytes, as in previous experiment. The cornua were removed, fixed and hardened, and carried through as usual, sectioned and stained with haematoxylin and eosin, to contrast the dilated, thinned walls of the right, with those of the normal left cornu.

The ovaries were also hardened and sectioned, to see if the distension and retention of the fluid in left cornu had any effect on the ovary of the same side.

MICROSCOPIC EXAMINATION. RIGHT CORNU.

The muscular layer of the walls is greatly thinned, being only a few fibres in thickness. The endometrium is very markedly reduced and consists merely of an undulating layer of epithelium, resting on a thin layer of connective tissue. The walls of transplanted part are similarly thinned.

LEFT CORNU is normal, the mucous membrane is a little thinned.

RIGHT OVARY shows the stroma and follicles staining well. The Graafian follicles and ova are seen/

seen in all stages of development. It is more vascular than the Left ovary, and shows relatively slightly more fibrous tissue. Weight 0·092 grms.

LEFT OVARY shows normal structure of young animal's ovary, well marked Graafian follicles and ova: all the tissue elements take the stain well. It is less vascular than Right ovary. Weight 0·083 grms.

Possibly the increased vascularity of the Right ovary is due to the increased resistance from the pressure in the distended cornu, throwing the blood back by anastomosis to the ovary.

Here one sees that the retained secretion has no demonstrable effect on the ovary of the same side. The secretion and dilation, moreover, is due to the action of the endometrium, and has taken place in the isolated and transplanted piece of the cornu, and is not referable to interference with the blood supply, nor is it dependent in any way, on its nerve connections - for these have been divided.

(Photographs 13 & 14)

EXPERIMENT II./

EXPERIMENT II.

THIS SECRETION is CONTINUOUS and CONSTANT and is not MATERIALLY AFFECTED by PREGNANCY.

A BLACK and WHITE RABBIT full grown, weight 2 Kilos. 240 Grms. was anaesthetised and prepared and abdomen opened under aseptic precaution. The Right Cornu ligated with silk ½" from its tubal end, and also at point 2½" from tubal end, - thus isolating the part between. A piece of the same cornu, at a point 1" from vaginal end, was brought out, through the abdominal wall and fixed, and the cornu opened and its margins stitched to the skin margins, thus establishing a fistula, to watch the state of the endometrium, from time to time.

Two days later, the fistula surface was moist, but the edges were beginning to become inverted, and two or three days later, the margins were quite indrawn, and the surface apparently dryish.

In ten days from date of operation, the fistula was prolapsed, the edges drawn in, and the wound/

wound dry and hard. The rabbit was quite healthy and well, but evidently pregnant. The animal continued in good health, and the fistula, examined from time to time, was always indrawn and dryish.

On January 7th,

Twenty-eight days after the operation, the rabbit looked ill, its coat rough and staring, and evidently making a nest, as if about to have young. No young were born, however.

January 10th.

Rabbit seems to be losing weight and in poor health - fistula dry, vagina pale, - animal is not doing well.

January 17th.

Rabbit eating well, but not in health. It was killed the following day, and on examination, weight was found to be 1 Kilo.980 Grms. The abdomen showed general pelvic peritonitis, with layers of lymph, which was easily separable, matting the right cornu to a coil of intestine. Three macerated young rabbits were found. One entirely free in the peritoneal cavity, and a large rupture in the distended cornu, between the ligatures, through which it had been extruded, and which exposed to view the other

two/

two foetal rabbits. The site between the ligatures had, at the time of ligation, contained three fertilised ova, which had developed, and at full time (January 7th) when the rabbit went into labour, the cornu ruptured: this, setting up peritonitis accounted for the ill health of the animal, observed at the time.

LEFT OVARY showed three well marked corpora lutea of pregnancy, the

RIGHT OVARY several ripe ovarian follicles.

The weight of the foetal rabbits was 46, 32, and 22 Grms. respectively, indicating that the ligatures had interfered more with the placental sites of the latter two.

This Experiment is instructive and indicates how uterine rupture may occur and pseudo-abdominal pregnancy be simulated. From it, one would be led to suppose also, that secretion of the saline fluid is arrested in pregnancy, for the fistula was apparently dry throughout, and of course, there was no evidence of hydrometra. My experiment here, had been performed on an already pregnant animal. The mere ligation did not prevent advancement to full term.

I/

I determined to repeat the experiment on a full grown rabbit, which I had taken precautions to know was not pregnant. (Photograph No. 15.)

The site of the rupture is interesting, it being on the surface furthest away from the placental pad - which, in the rabbit is on the surface which lies in contact with the mesometrium - as Young holds that the gradual thinning and rupture which occurs in ectopic pregnancy, is due to erosion by the advancing cells of the villi. The site of the villi in the rabbit is that most supported.

EXPERIMENT III./

EXPERIMENT III.

(FISTULA ESTABLISHED in NON-PREGNANT RABBIT)

February 2nd.

A BROWN and WHITE WELL GROWN RABBIT weight 1 Kilo 800 Grms. was anaesthetised and prepared under aseptic precautions. Abdomen opened and piece of Right cornu drawn out and incised longitudinally, and its margin fixed to the edges of the skin wound - fistula established, and the condition of the mucous membrane as regards secretion noted. Rabbit seemed quite well the following day. The fistula was examined frequently, almost daily, for the next fourteen days, and was always moist, and the rabbit was well. The fistula remained moist and gaping till February 23rd.

Three weeks after operation -

When coitus took place - and this was repeated three or four times during the next week. The fistula was moist but by -

March 6th -

was seen to be distinctly smaller and less secretion - the mucous membrane edges were becoming inverted and indrawn.

By the 10th March -

This/

This was still more marked, and the edges were now closely indrawn, but on separation, the same moisture of the surface was present.

The rabbit aborted two foetal rabbits on March 12th, and the mucous membrane remained indrawn for a day or two, and although the fistula seemed dryish, it could be opened up.

By the 19th March -

the fistula was opening and by the 24th, it was moist and the edges distinct as before pregnancy.

In the second week of April -

This rabbit again became pregnant, and on April 16th, when examined, the fistula was lessened in size, and showed the same tendency to indrawing, but not to the same extent. The surface was moist and the margins of the fistula approximated.

On May 10th -

Four foetal, full time rabbits were born. The fistula was moist and exuded blood, and on the 12th May, the surface was bathed with secretion but no blood.

The rabbit was well and was kept alive for several months, the fistula remaining patent and moist. This loss of secretion had no apparent effect on the animal's health, which, when dead, weighed

1/

1 Kilo 850 Grms. being thus slightly heavier than before operation.

This indrawing and apparent lessening of the secretion, is not dependent on the physiological changes of pregnancy, but suggests itself rather as anatomical and mechanical. This is due to the enlarging and thickening of the cornu, causing traction on the edges of the fistula. The swelling and thickening of the mucous membrane causing the edges to approximate, while the increase of the muscle which, in the unimpregnated cornu, takes place simultaneously with that of the pregnant cornu, the two cornua acting as one organ, causes the traction, and keeps the edges inverted. Thus, to all intents, the continuity of the channel is re-established, and the secretion passes down. This being so, the degree of indrawing should be less in an old established fistula, in which the edges were allowed to firm before pregnancy. This was illustrated in the following experiment.

EXPERIMENT IV./

EXPERIMENT IV.

February 12th.

RABBIT weight 1 Kilo.980 Grms.prepared as previously. The abdomen incised a little to right of middle line and the Right cornu drawn out and longitudinally incised - the edges carefuly stitched with the mucous membrane to the skin margins. A fistula was thus established. The healing was rapid the edges became firmly knit, and showed little tendency to inversion. The surface was frequently examined, and was always moist.

March 12th.

The margins were firmly fixed and adherent - no indrawing evident. The surface was moist and freely secreting, and the rabbit very well. This animal was kept a further month, and was then put to the buck, between dates April 12th to April 16th, and between these dates the surface of fistula remained moist.

April 22nd -

Surface still moist.

April 29th -

There are distinct swellings in Left cornu (pregnant).

May 4th -

Surface/

Surface moist, rabbit well.

May 8th -

Considerable secretion, weight of rabbit 2 Kilos 240 Grms.

May 12th -

Margins now beginning to invert and fistula moist though indrawn.

May 15th -

Three full time young rabbits were born, and the fistula exuded blood stained fluid. It has remained moist throughout pregnancy, and since its establishment in February 12th.

May 17th -

Fistula moist - no blood - during the last week of pregnancy the traction of the enlarging cornu was apparent.

The rabbit when killed showed no evidence of any peritonitis. It weighed 2 Kilos 90 Grms.

Photograph (No. 16.) shows the patency of fistula, after birth of three rabbits.

Sections of cornu were taken above and below the fistula for comparison. (Nos. 16-17)

Pregnancy, from the foregoing experiments does not appear to arrest this saline secretion, and the apparent drying is due to the indrawing, which, in/

in turn, is mechanical, and has evidently no physiological bearing.

To check these observations, a further fistula was established, as described in the following Experiment, and after being observed for two or three weeks - coitus, which resulted in pregnancy, was permitted, and the subsequent indrawing again observed - abortion followed and the rabbit was again put to the buck. Pregnancy followed, and went to full time, with results as previously recorded. The rabbit being healthy, after the lapse of a month, - during which time the fistula was frequently examined, and the surface always found moist, - was inoculated intraperitoneally with the serum obtained from the blood of a rabbit fourteen days pregnant, 5 cc.'s being injected. This produced a congestion of the vagina, but had no effect on the fistulous opening, and no indrawing at all was observed. A week later 5 cc.'s of serum of pregnant rabbit was again injected, but there was neither any indrawing nor diminution in size of fistula, nor in the amount of secretion.

EXPERIMENT V.

This clear, saline fluid, which is secreted regularly by the tubes and endometrium, and which from the first of the foregoing fistulous experiments seems to be somewhat lessened or arrested by pregnancy, and the margins of the fistula indrawn, is not actually arrested, as the surface of the fistula is always moist, as is seen by separating the margins. (EXPERIMENTS III. amd IV.) This is further strengthened by the following experiment, which combines and checks the results of the foregoing, and also strengthens the belief that the approximation of the fistula margins is mechanical, for it does not occur when pregnant rabbits' serum is injected.

JUNE 4th.

A FULL GROWN RABBIT weight 1 Kilo.950 Grms. was anaesthetised and prepared. The abdomen was opened and a fistula established in the Right uterine cornu. For three weeks, when examined, from time to time, the surface was always moist, and the margins of the fistula were well fixed, and the mucous edges everted.

JUNE 25th.

The/

Rabbit refused the buck, but two days later coitus took place.

JUNE 30th.

The margins showed indications of indrawing and slight inversion - the surface was moist. For the next week the fistula was still open, but smaller in size, owing to further indrawing, and on -

JULY 8th -

the animal aborted three foetal rabbits. The fistula was considerably indrawn, and the margins approximated, owing to traction from the growing uterus, and on casual inspection, looked as if closed. At the end of a week, after abortion, the fistula was distinctly open and surface moist.

AUGUST 6th.

Coitus again took place, pregnancy following, and by the 13th August again noticed distinct indrawing, but fistula open and moist. Rabbit very well, and at the 21st day after coitus, the secretion from the fistula was still evident. This continued till full term, when on September 6th, four young, full time rabbits were born, and blood exuded from the fistulous opening.

SEPTEMBER 8th

There was no blood from the cornual opening. Rabbit was quite well and healthy. Fistula was open and/

and moist, and on

OCTOBER 10th

rabbit was given 5 cc.'s blood serum from pregnant rabbit, injected intraperitoneally - no ill effects observed. Surface of fistula moist and bathed with secretion. The vagina was noted to be congested.

OCTOBER 17th

A further dose of 5 cc. of pregnant rabbit's blood serum given - no appreciable alteration on the size of margins of the fistula. The surface appeared, if anything, more moist for the two or three succeeding days after each injection.

It would seem, therefore, that the indrawing and approximation of the fistula margins, which occurs when pregnancy supervenes, soon after the fistula has been established, is due rather to traction consequent upon the growth of the uterine horn (muscle) rather than from any specific action of pregnancy in its effects on the body generally - for there is no indrawing when the pregnant serum is injected.

This animal used in EXPERIMENT V. remained well and healthy, and fistula open and moist for months, - was killed in February. Photograph shows Specimen with bristle in still patent fistula. (No. 18.).

EXPERIMENT VI.

HAS PREGNANCY ANY EFFECT ON RETAINED SECRETION IN THE CORNU AFTER DOUBLE LIGATION ? DOES IT CAUSE ITS RE-ABSORPTION ?

January 25th.

A FULL GROWN RABBIT which had a litter of five young on January 23rd, was anaesthetised, and the Right tube and Right cornu doubly ligated with silk. At the operation both ovaries showed corpora lutea, and numerous follicles, the whole uterus being congested.

FEBRUARY 9th

A swelling was detected in the region of the Right cornu, which was taken to be the distended isolated portion.

The animal refused the buck on 9th and 11th, but coitus took place several times on 14th February - although put to the buck on 19th and 23rd refused.

MARCH 2nd.

Foetal rabbits palpable in Left cornu.

MARCH 10th.

Still further enlarged and on the 16th March three young born.

MARCH 22nd, 25th, 29th, & 30th -

Put/

Put with buck but no coitus.

APRIL 1st.

The rabbit was anaesthetised and examined. Right cornu showed no evidence of any dilation, although the ligatures were apparently intact and had not cut through. (Silk used).

Both ovaries have ripe follicles. If the swelling felt was fluid in the ligated cornu, it had again been absorbed during pregnancy and it had in no way interfered with pregnancy.

In this rabbit the corpora lutea also seemed particularly well marked.

It was a strong rabbit, and having been carefully handled, I decided to re-ligate the Right cornu doubly with silk and stitched up carefully, putting some sterilised oil into the peritoneal cavity to avoid adhesions.

Coitus took place on May 2nd, - no young were born, so far as I could trace. A lump formed in the left iliac region, which was hard and curiously like a foetal rabbit.

The rabbit was very well, eating well, and fat. The lump persisted, and the rabbit was observed for several months and remained well, but refused the buck.

In January, February and March, the rabbit appeared/

appeared to be in oestral state, but did not take the buck until April 10th.

The lump in the iliac region persisted. The rabbit was well, no evidence of any impregnation having followed on coitus in April.

In August the animal was killed and examined, weight 1 Kilo 900 Grms. There was no evidence of any peritonitis. Right cornu was not dilated, no evidence of ligature.

Left cornu contained an almond-like body, but was not distended.

In the Left Iliac Fossa tucked away under a fold of peritoneum and bulging toward the groin, is a hard mass, calcareous in consistence, smooth, and unattached, except to the posterior wall, having no adhesions to any part of the uterus, bladder or rectum, and being some distance from Left cornu. A few adhesions to the layer of peritoneum over its site in the fossa were found.

On dissection this was found to be remains of foetal rabbit or rabbits. (Lithopoedion).

I could not trace the site of the rupture, if any, in the vornu.

On opening up the cornu an almost almond-like/

like body, about the size of a small hazel nut was seen, projecting into the lumen, adherent to the cornu opposite the mesometric attachment.

MICROSCOPICALLY the almond-like body consists chiefly of large numbers of spaces lined by columnar epithelium - these spaces vary greatly in size and shape. In places there are aggregations of epithelium in which the gland spaces are absent.

There is a varying amount of arealor connective tissue intervening between and supporting the glands. In places thin walled vessels are present.

On the surface of the mass, near its centre is a fissure - the surface of the nodule is covered by columnar epithelium. (Photographs. Nos.19-20 -)

The almond-like body probably indicated the site of rupture, for these bodies have been experimentally produced by causing a breach of the continuity of the mucous membrane. (Photographs Nos.21-22.)

EXPERIMENT VII/

EXPERIMENT VII.

DOES THIS SALINE SECRETION OCCUR IN TRANSPLANTED PIECES OF THE CORNUA ? IF SO, HOW IS THIS AFFECTED BY PREGNANCY ?

On February 1st

A WHITE (full grown) RABBIT, weight 2800 Grms. was anaesthetised and prepared. The abdomen was opened in the midline and 1½ inches of the Right cornu carefully, doubly ligated with silk and resected. The isolated piece having all its connections severed, was transplanted into the peritoneum of the right flank. The divided ends of the cornu were brought together and carefully reunited with silk sutures.

LEFT OVARY contained five recently discharged follicles.

RIGHT OVARY " several mature follicles.

The wound healed perfectly and the rabbit was quite well.

The rabbit refused the buck on February 19th.

March/

March 6th

Swelling was detectable in Right cornu, - its nature doubtful.

Coitus took place several times between the 16th and 23rd March.

29th March.

In left cornu could palpate three swellings size of a bean.

April 15th.

Rabbit well, weight 3 Kilos.70 Grms. and could palpate what seemed to be, two foetal rabbits to right of mid line, and three more to the left. Pregnancy well advanced, almost full time, but not with certainty, could I make out the exact number of foetal rabbits.

April 15th.

Animal anaesthetised and abdomen opened, found the transplanted part dilated and thickened, and like in all respects - to the naked eye - to the parts of the Right cornu, which did not contain young. The transplanted part, although distended, had not prevented the rabbit carrying young to the full time.

There were three well developed full time young rabbits in the Left Cornu, one practically in the vagina, showing that parturition was imminent.

In/

In the Right cornu, on the tubal side of the point of the section and ligation, were two young rabbits. These could not have been born, because of the cicatrical contraction at site of section of cornu.

It is particularly interesting to note, that the impregnation had taken place after the divided ends of the cornu had re-united and the lumen opened up, and the sperms had passed up, or else impregnation had been transperitoneally. This shows how unreliable is any form of sterilisation which depends on ligation or section of the tubes.

This experiment showed undoubted persistence of the fluid in the distended part, despite pregnancy, and also that such retained secretion did not cause abortion. (Photograph No.)

In EXPERIMENT VI. the fluid appeared to have been re-absorbed during pregnancy. This is not definite, for one must remember that the distension was assumed from palpation alone. In the only case in which Bond got absorption, he had likewise relied on palpation, for he states that the transplanted part became distended. He felt a swelling, but did not open the animal to see that it was the distended cornu, and although this disappeared with pregnancy, possibly it was not fluid.

In/

In my own experiments, in cases subsequently pregnant, where the ligated cornua were at the post mortem found undilated, the ligatures had cut through, and moreover, having relied solely, on palpation, I had no definite evidence that there had been any dilatations.

It is thus open to doubt, both in his and my own experiments, whether there was the distension. In his two other experiments, the results tallied with mine in EXPERIMENT VII. viz:- that the fluid persisted, even though pregnancy ensued. There was probably some degree of absorption, as owing to the vascularity that occurs during pregnancy, the absorptive powers of the parts are accentuated.

In the same paper Bond concluded that the secretion was arrested during pregnancy, and founded this on his fistula experiments, whereas in my instance, the fistula became less moist and the margins indrawn. From a careful examination of the fistula one found that it was always patent, and that, even after the animal had been twice pregnant, subsequent to its being established, the opening did not close. To my mind the indrawing is not dependent on lessened secretion, but to the degree of traction on the everted mucous membrane, which taking part in the growth of the cornu, generally,becomes swollen, and the /

the increase in the muscular pull -from the developing muscular elements in the cornual wall,-inverts the edges. The fluid, though still secreted, passes on down the lumen to the site of impregnation, and here bathes and swells the cells, which by a process of imbibition, form a bed for the developing embryo.

During the growth of the embryo, whose tissues require fluid, and whose nutrition depends on the establishment of an intimate relationship between itself and the lining cells of the uterus, which relationship is brought about by a gradual imbibition of fluid, which causes the cells to become vacuolated and opened up. The cells in the walls of the blood vessels becoming similarly swollen, the walls rupture and the blood bathes the attached surfaces of the embryo.

All this process demands an increasing amount of fluid. It is unlikely, therefore, that the secretion which is there normally in the unimpregnated state, should be arrested at a time, when it is particularly required. It is thus more likely to be actually increasedly produced. This would, furthermore, accord with the view that Bond later emphasises, that it is nutritive, - that being so, it is scarcely/

scarcely logical to suppose that it should be suppressed at a time, during which the nutritional state is required at its highest stage of perfection during gestation.

There are, however, at first sight some grounds for affirming that the secretion is arrested and does not in an occluded tube, accumulate, if the occlusion is brought about after pregnancy has begun, or at any period of gestation. This was the case in some experiments by Bond, and also in one performed by me, in which the cornu, on one side, was doubly ligated with silk, within four days of coitus, from which impregnation in the other cornu took place, - here the lining membrane in the isolated part became swollen, but there was no distension by fluid. This does not necessarily mean that the secretion of the saline fluid was arrested, but only that, as in all cases of pregnancy, the parts were more vascular and thus absorption took place more quickly, so that at no time was there any excess of secretion. Moreover, the extra blood supply, and hence the fluids generally, are diverted to the sites of impregnation in the other cornu, here to supply the great needs of rapid development and growth, viz:- fluid/

fluid. It is not perfectly good reasoning to assume that because it is not evident by distension, that the fluid is arrested, for, if pregnancy is allowed to go on to term, one finds that within fourteen days after parturition, the ligated cornu dilates, always provided that the ligatures are intact, and have not cut through. It may not be manifest during pregnancy, because absorption keeps pace with secretion.

The foregoing EXPERIMENTS VI. & VII., are not very definite or conclusive as to the effect of pregnancy on the accumulation or subsequent re-absorption of the saline fluid in a doubly ligated cornu. I, accordingly, decided to doubly ligate both cornua, and, without allowing any time for distension, also to inject the blood serum of a pregnant rabbit, intraperitoneally, and to see whether the ligated parts filled with fluid, on the assumption that the substances elaborated at the site of the trophoblast are conveyed throughout the body by the blood stream.

EXPERIMENT VII.B.

EXPERIMENT VII.B.

INNOCULATION WITH SERUM FROM PREGNANT RABBIT SIMULTANEOUSLY with DOUBLE LIGATION of BOTH CORNUA.

24th October.

A WHITE (full grown) RABBIT, weight 2 Kilos.600 Grms. was anaesthetised and prepared. Abdomen was opened and both cornua doubly ligated with strong silk at extreme tubal and vaginal ends, and wound closed and healed by first intention.

OCTOBER 31st.

The rabbit was given 2 cc. of blood serum from animal in first week of pregnancy.

NOVEMBER 4th.

Another 2 cc.'s of the serum was injected, the following day small swelling palpable in cornua.

NOVEMBER 8th.

Rabbit was well. Vagina congested and coitus took place. Weight 2 Kilos 550 Grms.

NOVEMBER 12th.

2 cc.'s serum given. Rabbit very well and the swelling is now the size of a bean in each cornu.

NOVEMBER 22nd.

Weight/

Weight 2 Kilos.550 Grms. A further 2½ cc. serum from pregnant rabbit given. 23rd and 25th refused the buck.

NOVEMBER 28th.

5 cc.'s of blood serum from rabbit fourteen days pregnant was injected. The weight was 2 Kilos.800 Grms. Swelling in Right cornu is now slightly larger and distinctly cystic. In the left cornu it suggested full time pregnancy, almost.

DECEMBER 3rd.

Rabbit very well. Abdomen distended and the cystic swelling like pea-pod (shape elongated oval) in region of Right cornu. On left side palpation suggests two or three full time foetal rabbits. This is difficult to harmonise, unless pregnancy existed at the time of ligation. During December the rabbit remained in good health. The swellings in the region of cornua persisted, and in the Left was very like pregnancy, in fact seemed quite definitely so. The animal was given 5 cc.'s pregnant rabbit's serum.

During January a similar condition was found, the swellings getting a little smaller, if anything. Rabbit weighed 2 Kilos 500 Grms. on January 20th and was given more serum intraperitoneally./

intraperitoneally.

In February the weight was constant at 2 Kilos. 450 Grms., but rabbit seemed in less healthy state. Swellings seemed harder to palpation, but certainly no larger.

FEBRUARY 19th.

The animal was given 10 cc.'s serum from rabbit 18 days pregnant. It was kept a further week and, as there had been no change in the swellings in the abdomen, so far as could be detected on palpation, I decided to kill and examine it.

FEBRUARY 27th.

The Rabbit weighed 2 Kilos. 450 Grms. and on palpation, before killing and opening, I was fairly convinced that I could detect two or three foetal rabbits.

On opening the distended left horn presented itself greatly enlarged, and carrying three mature foetal rabbits, which had perished, between the ligatures. On the right side, and co-existing with the pregnancy, was a well marked hydrometra. (Phtographs Nos.23.-24)

This was most instructive, for here one had a rabbit, in which hydrometra was present, despite the fact that the animal waspregnant at time of/

of ligation of the cornua, and in addition had been treated with pregnant rabbit's blood serum. It might have been contended that the effect of pregnant serum, could not possibly have been similar to actual pregnancy, but here the pregnancy existed also, and there can be no doubt that the hydrometra formed subsequently to pregnancy, for there was none at the time of ligation. The pregnancy, though very early, must have been present, though undetected. This was more conclusive that I had hoped for, and definitely disproves Bond's suggestion, that the saline fluid is arrested during pregnancy, or that, if hydrometra exists, it must have been prior to pregnancy.

The Right cornu was sectioned to show the thinned walls. The Left illustrated the very marked hypertrophy that occurs during pregnancy, and when futile attempts are made to expel any resistance in the cornu. This lends support to my suggested explanations of abortions which occur in cases of hydrometra:- viz. that the effort to force on the fluid - which by its distension of the Uterine Wall, produces probably very much the same subjective sensations, as occur from distension by pregnancy - sets up contractions at the sites of the engrafted/

engrafted ova, and the attachment is weakened, and abortion ensues. It is not, as has been suggested, due to any property of the absorbed saline fluid.

MICROSCOPICALLY.

The Right Cornu shows appearances very like those already described for similar condition of hydrometra. (Photograph No. 25.)

The Left Cornu shows the very marked hypertrophy of all the muscular layers - the endometrium is thickened and there is a distinct decidual change. (Photograph No. 26.)

EXPERIMENT VIII./

EXPERIMENT VIII.

LIGATION OF CORNU in NON-PREGNANT RABBIT when not FOLLOWED by DISTENSION is due to LIGATURE HAVING CUT THROUGH.

A WHITE (Rough haired) RABBIT, weight 2 Kilos 530 Grms. This rabbit had been running with the buck, and was experimented upon with the object of determining whether the isolated part distended (assuming the rabbit to be pregnant). The animal was anaesthetised, prepared and the abdomen opened in mid-line with aseptic precautions.

The Right ovary contained five recently ruptured follicles, and the

Left Ovary two or three ripe follicles on surface, with extravasated blood (dark blackish-red).

The Right Cornu was doubly ligated with silk and the Right tube also doubly ligated.

I could not detect any evidence of engrafted ova in the Left Cornu, though it was much congested and somewhat thickened.

The Vagina was congested and moist. There was a possibility of pregnancy in the Left Cornu. The abdomen was closed.

In a fortnight, the rabbit being very well, was/

was put with the buck but refused. At the end of three weeks, the Right cornu on palpation seemed to be dilated. Coitus took place twice, within a month from date of operation. Seven weeks after operation the animal was not looking well, and was accordingly killed, two months after the operation. No young had been born.

At the post mortem, the ligated Right Cornu and tube were undistended, and the Left cornu was distinctly thickened and larger than the Right.

To the naked eye appearance, the ligatures were apparently intact in Right Cornu. On splitting up the cornu longitudinally, however, the ligatures were evident, and although the walls seemed to be in contact, one ligature was seen to project from the wall internally, the lumen being this re-established. (Photograph Nos.27-28)

The Left Cornu showed thickened walls, and there was an exuberant overgrowth of the mucous membrane.

One/

One sees, therefore, that there is almost invariably distension of a ligated cornu, even though ligated subsequent to pregnancy, and that those cases in which pregnancy follows, and there is no dilatation, are probably explained on the same ground as non-pregnant ones, viz:- that the ligatures have cut into the lumen. At the same time, when distension and pregnancy are present, while there may be a tendency to partial re-absorption, there is no evidence of any inhibition or specific effect of the trophoblast on the formation of the fluid; but rather to an increased absorption, - and this ensues, owing to an accentuated metabolism, which is evident in all tissues, consequent upon and coincident with, the embedding of an ovum. This explanation also holds good regarding the lessened moisture of the surface of the fistula in the cornu, that occurs during pregnancy.

The secretion occurs in transplanted portions of the cornu and is thus independent of all nervous influence. It is suggestive that this fluid is nutritive and protective. As the ova are shed and drawn into the Fallopian tube, this fluid surrounds/

surrounds them, and may be in the mammal, nourishes the ova, till they have become embedded. The value of the normal saline solution is well recognised, and it is likely, from the chemical resemblance, that the secretion acts on the ovum as the ordinary blood plasma does, in nourishing the more mature tissues of the body.

The fluid secretion in the Fallopian tube in the human female contains 1% of sodium chloride, and the specialised changes in the Uterus with its thick endometrium on its specialised muscularis mucosae, enable the uterine lining to act as a sponge and absorb this fluid, as it passes over the surface, thus nourishing and swelling the cells; and when they are, so to speak, full to overflowing with this secretion, they become teased out at the deeper strata of the mucosae, and the separation opens up the vessels and menstruation occurs. In the event, however, of an impregnated ovum finding a lodgement, the fluid is diverted to the trophoblastic site, and goes to nourish it. The rise and fall, therefore, of this fluid, which is continuously secreted, may in some measure explain menstruation. Menstruation, however, is supposed to be dependent on/

on ovarian function, though this view from certain clinical facts, is by no means unassailable.

Is there, then, any relationship between the ovarion function and this secretion? Have the Ovaries any effect?

To answer these questions I performed partial and complete ovariotomy.

EXPERIMENT IX./

EXPERIMENT IX.

PARTIAL OVARIOTOMY DOES NOT PREVENT DILATATION on the LIGATED CORNU on the SIDE of the REMOVED OVARY.

A BROWN RABBIT, weight 2 Kilos.530 Grms. was anaesthetised on December 17th, under aseptic precautions and abdomen was opened.

The uterine cornua were both small and slender. Both cornua were doubly ligated, and the ovary on the left side was removed. Its weight, on removal was 0·03 Grms. The rabbit recovered, and was in good health.

JANUARY 4th.

Rabbit well. Vagina congested and suggests oestrus.

JANUARY 17th. Vagina congested - suspicion of swelling on right side - not definite on left side.

JANUARY 26th.

Rabbit was examined. Weight 2 Kilos.560 Grms. Both cornua were distended with clear fluid. The Right the more dilated and distended. Right Ovary 3½ times the size of the Left. The Left cornu, although dilated and contained fluid, yet not/

not to the same extent as the Right cornu, - it was only half the size, in fact.

The Right ovary weighed 0·295 Grms, and shows numerous, ripe, Graafian follicles. (14 were counted). (Photographs 29-30.)

MICROSCOPICALLY. The Left ovary showed structure of normal gland in well grown young animal, - many primordial ova and Graafian follicles.

The Right ovary showed marked increase of stroma and of the cellular elements - well marked ova and Graafian follicles and corpora lutea. The stroma is proportionally more hypertrophied than the follicular elements, which were relatively fewer than in the left ovary.

Under the high power the nucleus with necleoli seen in some maturing ova, and in the Graafian follicles in the deeper layers of the membrana granulosa, blood has been extravasated.

CORNUA both show thinning of the endometrium and also of the muscular coat in the walls. The Right cornu had these changes more marked - appearances similar to those already described in connection with hydrometra.

Here/

Here the removal of one ovary had no appreciable effect on the cornu of same side. Note the compensatory hypertrophy of ovary, evidently both of stroma elements and follicular structures. This is referred to later.

Although the cornua both contained this saline fluid, under pressure this did not interfere with the ovary growth, which is accentuated.

EXPERIMENT X./

EXPERIMENT X.

COMPLETE OVARIOTOMY DOES NOT PREVENT DISTENSION OF LIGATED CORNUA.

A BROWN RABBIT, weight 2 Kilos 510 Grms. was anaesthetised on March 24th. Abdomen was opened and both cornua ligated doubly with silk ligatures. Both ovaries completely removed. Wound healed by first intention. The rabbit kept in good health till September 23rd, (6 months later) and was then examined. Both cornua were distended with clear fluid between the ligatures. The cornua here show condition of walls apart from dilatation, 6 months after double oophorectomy.

MICROSCOPICALLY. The Right Cornu shows a thinning of the walls. The endometrium has its cells flattened, the muscular elements are thinned and teased out as it were, owing to the distension. The elements stain fairly well. The muscle cells show, however, a tendency to fainter (acid) staining than usual. The nuclei are somewhat crowded together, and there are patches of degeneration. The mucosa is/

is thin and the mucosal glands are few and small, while the connective tissue is increased in amount.

In some sections, the histological changes in the mucous membrane are more marked, and the overgrowth of connective tissue has almost obliterated the mucosal glands.

The Left cornu shows less marked changes, and the degenerative processes are comparatively slight, seeing that this is 6 months after complete oophorectomy.

(Photograph No.31.)

EXPERIMENT X. A./

EXPERIMENT X./A.

THE UTERINE CHANGES FOLLOWING DOUBLE OVARIOTOMY are not PREVENTED ALTHOUGH the ANIMAL is TREATED with CORPORA LUTEA and OVARIAN EXTRACT.

DECEMBER 20th BLACK (Smooth haired) RABBIT was anaesthetised and prepared, both ovaries were removed, through an incision in the mid-abdominal line. Weight at time of operation was 1 Kilo 980 Grms. The abdominal wound healed aseptically and the rabbit being fat and well, was treated with extract of corpora lutea and ovarian extract periodically, throughout the ensuing year.

APRIL 10TH.

Almost four months after both ovaries had been removed, this rabbit was covered by the buck.

SEPTEMBER 26th.

The animal weighed 2 Kilos.200 Grms. and was then getting a dose of corpora lutea equal to 30 grains of the fresh gland.

At the end of the year, the animal seemed to be losing weight. Its coat was shining and glossy, and/

and its general health very good, it being very brisk and lively.

NOVEMBER 20th.

The rabbit was fat and well, weight 2 Kilos 100 Grms. and when put to the buck fought him savagely - no coitus.

I now combined pregnant rabbits' blood serum, with the ovarian treatment and gave 2½ cc.'s of serum from rabbit seven days' pregnant, and on NOVEMBER 27th,

a week later gave 5 cc.'s serum from fourteen days' pregnant rabbit. Weight was now 2 Kilos 140 Grms. Coitus took place on the evening of the same day.

Further doses of pregnant sera and ovarian extract were given, and the animal was killed and examined on January 20th. It was fat and well nourished. The Uterine cornua were atrophic. (Photograph No.32.)

Here neither the pregnant serum nor ovarian extract had prevented the atrophic changes, which rather indicates that other factors than mere removal of the ovaries are at work, - probably the withdrawal of the periodic exercise, viz:- contractions which occur at the oestral state in normal rabbits.

MICROSCOPICALLY/

MICROSCOPICALLY. Note the great reduction in the size of the uterus. It is little larger than a Fallopian Tube. There is great thinning of the muscular layers. The mucous membrane is atrophic, most of the glands have disappeared, and there is an increase of the connective tissue elements.

The treatment with the ovarian and luteal extracts had quite failed to prevent these histological changes - suggesting that the atrophy is, to some extent, one of disuse.

EXPERIMENT XI./

EXPERIMENT XI.

HYDROSALPINX AFTER REMOVAL OF BOTH OVARIES.

A WHITE FRENCH RABBIT, weight 2 Kilos 870 Grms. was anaesthetised on December 9th and abdomen was opened. Both cornua showed several constrictions, 9 on the right side and 6 on the left. Both ovaries were removed and left Fallopian tube doubly ligated with silk. The wound healed rapidly, and the rabbit did well. Three months later the animal was killed and examined. The left tube was enlarged and distended to the size of a goose quill. Here again, the removal of the ovarian influence had had no retarding effect on the secretion of the tube.

The constrictions of the cornua and also the hydrosalpinx are shown in the photograph (No.34)

MICROSCOPICALLY.

The cornual walls after the removal of both ovaries 3 months previously. The mucous and muscular layers show very little departure from normal - there is no evidence of degeneration, except in/

in a little thinning of both layers.

The lumen of the cornu is expanded and in the centre almost entirely filling it up, there is a mass which consists of expanded glandular spaces, lined by large columnar cells. The surface of the mass is covered by similar cells. The condition is obviously an adenomatous polypus. This is very interesting, in view of the idea which has been advanced by some investigators - Hitschmann & Adler - that in the human, the increase in the glandular tissue in the pre-menstrual phase, is dependent upon increased activity of the ovaries at that time. Here we have an evident glandular hyperplasia, although we have no ovarian tissue whatever. (Microphotograph No.35.)

From the foregoing experiments 9, 10, & 11, it is shown that removal of the ovary does not prevent the distension following ligation. In experiment 9, one sees that there is a difference in the degree of distension - the cornu on the side of the removed ovary, being less dilated. This may be explained by the fact that with the removal of the ovary, the blood supply required for that side is less, the ovary blood being diverted.

Similarly, the removal of both ovaries did not prevent the ligated cornu, and also the ligated tubes/

tubes becoming distended. This, then, seems definite, and accords with the observations of Bond. It, however, opens up the question - if this function, viz:- The secretion of the saline fluid by the endometrium - is uninfluenced by the ovary, should the Uterus itself be influenced by ovariotomy? (EXPERIMENT XI.A.) It has been pretty definitely stated that the uterus atrophies, and degeneration sets in after removal of the ovaries, but there still seems to be considerable evidence clinically, and some at any rate, experimentally, which shows that in some individuals the uterus is not dependent on the functional integrity of the ovaries, - or at any rate, that it continues to pass through the changes of the menstrual period.

It was noticed in all the experiments in rabbits, that there was an increased tendency to abortion, during the first pregnancies, subsequent to operation. This was described by Bond to be a feature of those cases, in which pregnancy occurred, while the saline fluid was in the distended tubes of cornua, and he held that it was "due to absorption "under pressure of the retained fluid", which he thought in some way inhibited the growth of lutein tissue in the ovary, by counteracting the stimulus of the/

the substance (hypothetical) produced at the site of the trophoblast, and that this stimulus was conveyed by the blood stream. Abortion was also of frequent occurrence, in my experiments, in the production of uterine fistulae, in which there was no retention and hence no absorption of the saline fluid, but rather a draining away.

This is a point very difficult of demonstration, and necessitates the transplanting of the ovary and production of hydrometra, and then the incidence of pregnancy. In my experiments on this point, I had little success, as I found that in all cases ovarian grafting was only of very doubtful permanent success. All grafts undergo atrophic degeneration, the follicles suffering first, the interstitial and stroma cells, after a time, seem subsequently to revive, and regain vitality. This tallies with the observations of Limon. Marshall & Jolly, however, appear to have had almost absolute success in Rats.

In my experiments of transplanting, there was, so far as I could demonstrate, no evidence of any ovarian tissue after 11 months in rabbits. There would seem, therefore, to be a progressive degeneration from the first in transplanted ovaries in rabbits, varying in degree and influenced by the site, intramuscular/

intramuscular graftings being more successful and less likely to undergo early degeneration than those on the peritoneum. With these changes going on, it cannot be of much value to consider incidental changes occurring also, as due to any effect of retained secretion, for one cannot eliminate the disturbing factor of the transplantation.

I have, therefore, not given these experiments in detail, feeling that it was quite impossible to eliminate the degeneration and changes due to transplanting, from those (if any) arising in the transplanted gland, as the result of special conditions in the womb - such as distension with the saline fluid.

It is, however, probable, that the effects of uterine influence on ovarian changes and function are brought about by the substance or substances developed in the uterus, being conveyed by the blood stream. The Mammary changes of pregnancy, however, have been shown by Starling, to be dependent on a substance developed in the body of the developing embryo. (Mammary hormone).

THE/

THE EFFECT of this RETAINED UTERINE SALINE SECRETION on the OVARIES. HOW DOES IT INFLUENCE THEM?

It is well known that the presence of a living trophoblast in the uterus, determines the active growth of luteal tissue and ovarian hypertrophy, and that this reaction is due to a definite substance or substances, produced by the trophoblast, at the site, and influenced by the site. The uterine endometrium normally providing the best site, - is probable, because in cases of pregnancy occurring abdominally - or in the broad ligament, where there is no endometrium, or in the tube, where the lining is without glands, we find the ovarian changes less marked, and the corpora lutea very poorly developed: and in ovarian pregnancy, only very rarely, is any lutein tissue found at all.

Bond has shown that the stimulus which determines this, is conveyed, not by any nervous impulse, but by the blood stream. That being so, the blood plasma of a pregnant rabbit should contain this stimulus and promote the growth of lutein tissue in the ruptured follicles of an ovary.

It has further been shown that this lutein tissue is necessary for the continued nutrition of the/

the trophoblast, in the first early stages of gestation, till the placenta is formed. (Marshall & Jolly)

Bond suggests that the retained uterine saline secretion, as in hydrometra, antagonises this stimulus, and this inhibits luteal tissue growth, with the result that abortion occurs frequently in cases of pregnancy, following on distension of the tube or cornu. If abortion was due, in these cases, to absorption of the saline fluid, and its inhibiting effect on the ovary, then one would expect that the results would be more evident, when the saline fluid was injected intraperitoneally, into a pregnant rabbit - a rabbit so treated, however, carried its young till full time, and the ovary is that of a normal full time pregnant rabbit. (See EXPERIMENT XI.B.)

EXPERIMENT XI.A.

HYDROSALPINX AFTER DOUBLE OOPHORECTOMY 14 MONTHS PREVIOUSLY.

A BLACK & WHITE RABBIT (Dutch), weight 1 Kilo 900 Grms. was anaesthetised on December 27th, and both ovaries removed, and the right Fallopian Tube double ligated with silk. Healing was aseptic, the rabbit remained healthy and became very fat. When killed the Right Tube showed marked Hydrosalpinx. The cornua were attenuated. Complete removal of the ovaries, in this case, had not prevented the secretion of the saline fluid and distension of the tubes. (Photograph No. 36.)

MICROSCOPICALLY.

Both cornua are markedly shrunken and atrophied - the lumen is reduced in size to about that of the lumen of the Fallopian tube. The muscular layers are thinned, the fibres broken up, and the connective tissue increased.

The mucous membrane shows a great over-

overgrowth of fibrous tissue and the glands are scarcely to be seen.

The sections show congestion of the vessels between the muscular and mucous coats.

The tissues, although atrophic, all take the stain well.

(Photograph No. 37.).

EXPERIMENT XI.B.

INFLUENCE ON HEALTH OF RABBIT BY THIS SALINE FLUID.

TWO RABBITS of the same litter, weighing:- A. 2 Kilos.150 Grms. B. 1 Kilo 990 Grms. were kept under identical conditions and put to the same buck.

A. was given 1 cc. of the saline secretion from hydrometra intraperitoneally, during the first, second and third weeks of gestation.

B. was given 1 cc. of normal salt solution at similar times.

A. gave birth to 4 young rabbits, average weight 40 grms.

B. gave birth to 3 young rabbits, average weight 36·5 Grms.

Here it is seen that actual intraperitoneal injections had no ill effect - the rabbit carried young to full time and the ovaries showed normal development of luteal tissue, as in full time pregnant rabbit. (Photograph No. 38. & Micro-photograph No.39)

Weight of Right ovary from Rabbit A. was 0·435 Grms.

Weight/

Weight of corresponding ovary from Rabbit B. was 0·412 Grms.

MICROSCOPICALLY.

The ovary of Rabbit A. shows particularly well developed corpora lutea - the luteal cells being very large and the neclei well staining - there is not the slightest evidence of any retarded growth.

Again an animal in which hydrometra is produced and pregnancy co-exists - or which is subsequently treated with intraperitoneal injections of pregnant rabbit's blood serum, should show a departure from the normal growth of luteal tissue in the ovary. In Rabbit used in EXPERIMENT VII.B, the distended Right cornu is evident and pregnancy in the Left cornu had gone to full time, which suggests that there had not been any inhibition in the growth of the luteal tissue by the hydrometra. And, further, the blood serum from pregnant animals, by virtue of its containing this substance elaborated at the site of the trophoblast, when injected into normal animals, should induce the growth of the luteal tissue in ruptured ovarian follicles. This was done in Experiment with Gray and White rabbit after hysterectomy/

hysterectomy and examination of the ovaries made. The experiment is later recorded. Luteal tissue in both ovaries was well marked.

The tendency to abortion is probably not due to any definite action of the retained saline fluid or the lutein tissue, - (in support of which Bond furnishes no evidence) but rather, it would seem to be the outcome of abnormal reflex stimuli, due to the distension of the uterus, by the fluid, the uterus endeavouring by contraction to force the fluid on, also sets up contractions about the sites of the engrafted ova and they are expelled. The distension producing the same subjective sensations to the rabbit, as would be produced by a distension of pregnancy. It is thus a mechanical, rather than a physiological result, for, as I have pointed out, no changes are noted from absorption of the fluid, when injected intraperitoneally, (Rabbit Experiment XI.B) the factor wanting being the irritation and tension in the cornu when distended.

THE/

The retained fluid has been held to be a factor in the production of adenomata in the cornual endometrium in the rabbit.

These are said to form at the site of abortive engrafted ova (Bond). In experiment VI., I have noted an adenomatous body in the cornu, probably at site of rupture - in this rabbit there was no distension nor retained fluid. There was, however, the breach of continuity of the endometrium. Loeb pointed out that at certain periods after ovulation, principally from the fourth to eighth day, any cut dividing the surface endometrium and exposing the glandular elements, was liable to produce an overgrowth of adenomatous tissue at the site of injury, and he attributed this to a predisposing substance secreted by the ovary.

The development of these bodies cannot, therefore, be attributed to the retained saline secretion, but rather to the reflex stimuli from the seat of damage to the endometrium by the separation of the engrafted ova. It is suggestive that for a few days after the stimulus of coitus in the rabbit, the endometrium secretes a special substance which promotes the growth of glandular tissue and this is the/

the period during which the cavity of the ruptured ovarian follicle is being rapidly filled with luteal cells - and these, by their special active proliferation, may furnish to the blood a substance which stimulates the glandular growth in the uterus, and thus forms the thick succulent endometrium for the embedding of the ovum, thus poor development of corpora luteal tissue will give a correspondingly poor development of the endometrium which furnishing an insecure bed for the ovum, leads to its being shed. (Abortion).

EXPERIMENT XII.

COMPENSATORY HYPERTROPHY OF OVARY.

One found that in EXPERIMENT IX., after removal of the Left Ovary, which weighed 0·08 Grms., the other hypertrophied and weighed 0·295 Grms. Does this always occur? Or under what conditions?

Bond holds that in order to get compensatory hypertrophy of the ovary, coitus was necessary, and that it did not occur otherwise.

Marshall & Carmichael got compensatory hypertrophy in cases where no coitus or pregnancy was permitted.

In EXPERIMENT IX. there had been no coitus and the enlarged condition of the remaining organ cannot thus be due to any added condition of pregnancy.

A. BLACK & WHITE RABBIT (Young) weight 1 Kilo 400 Grms. was prepared and anaesthetised on July 7th. Abdomen was opened and the Right ovary removed. The animal was not pregnant.

Ovary weighed 0·09 Grms.

The rabbit remained in good health and 5½ months/

months later was examined and weight was 1 Kilo 980 Grms. No evidence of any peritonitis. There was a hydrosalpinx on right side (side of removed ovary). Left ovary showed marked hypertrophy. Five ripe and bursting Graafian follicles and several corpora lutea shown on surface. Weight of Left ovary 0·490 Grms. Here no coitus had been allowed - the remaining ovary however, has increased $5\frac{1}{2}$ times in size, within 6 months from date of removal of first ovary.
(Photograph No. 40.)
MICROSCOPICALLY.

Right ovary shows structure of normal ovary.

Left ovary shows all the elements of an active healthy ovary. Primordial ova in the subcapsular region and ovarian follicles in all stages of development.

Also well marked luteal tissue, and increase of the ovarian stroma.

The hypertrophy noted here is undoubtedly due largely to a formation of luteal tissue, but no coitus had been allowed, and therefore can definitely exclude pregnancy.

Luteal tissue formation in this rabbit has thus occurred irrespective of ovulation.

B. The/

B. BLACK RABBIT. (White left front leg) full grown, weight 1 Kilo 900 Grms. prepared as previously and abdomen opened July 7th. The Right ovary was removed, was well developed and showed numerous ripe ovarian follicles, weight 0·315 Grms. The animal was kept several months and remained healthy. Twelve months later coitus was permitted, and the Left ovary subsequently examined, it weighed 0·510 Grms and showed very nicely the compensatory enlargement. On the surface one sees several mature follicles, clear and distended, and opaque yellow spots of the corpora lutea. Two or three of the follicles were dark and haemorrhagic. (Photographs Nos.41 & 43.).

MICROSCOPICALLY.

The Right ovary shows normal structure follicles in various stages of development, and well developed interstitial tissue.

The Left ovary shows striking difference from the Right, there is a marked increase of stroma with comparative absence of follicles, and scattered throughout the section, are the remains of hyaline degenerated follicles.

This is obviously a true hypertrophy and due to increase of the stroma almost entirely.

The cornu is cut obliquely, and this shows a/

relatively greater quantity of muscular and mucous tissue, but is otherwise normal

C. The compensatory hypertrophy in the full grown rabbit is not dependent on coitus, or pregnancy for in the following, the first ovary was removed during pregnancy on the tenth or 11th day, and the other examined many months afterwards.

BLUE GRAY (Smooth-haired) RABBIT fully grown, weight 2 Kilos 270 Grms. was prepared and anaesthetised on July 7th, and the Right ovary removed. The Right cornu contained two foetal sacs, the Left cornu contained two foetal sacs also (probably 10 days). The abdomen was closed and the rabbit went to full time without aborting.

Weight of Right ovary 0·24 Grms. This represents the added growth of pregnancy. The foetal rabbits at term each weighed about 44·4 Grms. Those in the right horn on the side of removed ovary and corpora lutea controlling them, were equally nourished, and as well developed as those in the opposite horn.

The rabbit remained healthy and well but was not allowed to again become pregnant and the Left ovary was examined several (12) months later, and showed/

showed weight 0·385 Grms. The two ovaries are shown in (Photograph No. 42.) Note the corpora lutea in the Right ovary (pregnant) and Graafian follicles in the Left (non-pregnant) ovary.

One sees here, that the controlling influence of the corpora lutea is only absolutely essential to the ovum in its early stages, and that in rabbits probably ceases to be so within the first week of gestation.

MICROSCOPICALLY.

The Left hypertrophied ovary shows comparatively few ova and follicles, but there is a marked increase of the stroma.

At one pole a very pretty fully developed Graafian follicle with ovum and nucleus is seen, with the discus proligerus , which is seen to extend as a band of cells, extending right across the follicle, with the ovum in the centre. (Photograph No. 5.)

The Right ovary has the appearance of a 10 or 12 days pregnant ovary. The luteal tissue cells are seen arranged in columns, running in from the follicles. Irregular vascular spaces are seen in the walls round the corpora lutea.

EXPERIMENT XIII.

THERE ARE CONDITIONS UNDER WHICH NO COMPENSATORY HYPERTROPHY FOLLOWS REMOVAL OF ONE OVARY.

FULL GROWN OLD RABBIT (White and black with blue eyes) weight 2 Kilos 900 Grms. was prepared and anaesthetised on June 6th. Abdomen opened and Right ovary removed, weight on removal 0·57 Grms. Abdomen was closed and healing was aseptic. The Rabbit remained in good health and was killed six months later. The Left ovary was congested and contained twelve to fourteen ripe ovarian follicles. There was no compensatory hypertrophy, however, the weight being 0·555 Grms - barely $8\frac{1}{4}$ grains.

MICROSCOPICALLY.

Sections show a few follicles - but chiefly ovarian stroma.

EXPERIMENT XIV./

EXPERIMENT XIV.

EXPOSURE TO X RAY PREVENTS COMPENSATORY HYPERTROPHY.

JUNE 26th. A well grown young BLACK & WHITE RABBIT (in toed) weight 1 Kilo 500 Grms. was treated with definite doses of X Ray 0·5 H of Sabouraud dose being given at intervals of 3 or 4 days, five such doses being given. The rabbit was then anaesthetised and prepared, and the Right ovary removed which weighed 0·157 Grms. The animal was carefully stitched up and made an excellent recovery and was kept for six months, during which time it was perfectly healthy. It was then killed and the Left ovary removed and examined and found to weigh only 0·155 Grms. There were several follicles on the surface. The weight of the animal when killed was 1 Kilo.970 Grms., - showing that it had gained considerably in weight. There was no peritonitis. (Photograph No. 45.).

MICROSCOPICALLY.

The ovary is congested. Ova are seen in the subcapsular region - they are irregular in outline/

outline and seem to have shrivelled. The follicles are irregular in outline and the membrana granulosa layer is broken up.

EXPERIMENT XV./

EXPERIMENT XV.

DEFINITE DOSES, OF X RAY APPARENTLY ARREST OVARIAN GROWTH.

JUNE 6th.

THREE YOUNG RABBITS from same litter, six weeks old, each weighing 790 grms. were taken. One was kept as control and the other two given doses of X.ray.

A. was given two full Sabouraud doses and B. one full Sabourand dose.

JULY 16th.

A. which had received two full doses and was looking thin, was killed. The Ovary, Thyroid and Adrenal were examined. The Ovary weighed 0·03 Grms, the Adrenal 0·065 Grms, and the Rabbit 650 Grms.

The Control was killed at the same time and the ovary weighed 0·085 Grms. The Adrenal 0·110 Grms. and the Rabbit 1200 Grms.

Rabbit B. was killed on June 21st, 14 days after the single full Sabourand dose. The ovary weighed 0·03 , Adrenal 0·07 Grms and the animal 800 Grms.

The annexed Table shows results.

TABLE/

T A B L E .

	KILLED	WEIGHT of OVARY	WEIGHT of ADRENAL	WEIGHT of THYROID	WEIGHT of RABBIT
CONTROL.	July 16	0·085	0·110	0·075	1200 Grms.
2 Doses. A.	" "	0·03	0·065	0·0365	650 "
1 Dose. B.	June 21	0·03	0·075	0·035	800 "

NOTE. All growth of ovary in A. seems to have been arrested by the first full Sabourand dose of X. Ray, and the uterus had its growth similarly arrested. (See Photograph No. 46.)

It is thus seen that X.Ray can prevent hypertrophy, in fact in young rabbits it apparently arrests growth and development of all the glands.

MICROSCOPICALLY.

RABBIT C. Normal growing rabbit's ovary. Note the great number of young ova.

RABBIT A. The ovary shows marked changes. The follicles are broken up and the cells of the membrana granulosa disintegrated.

All the ova are shrunken and irregular. The fibrous tissue in the stroma is increased.

RABBIT/

RABBIT B. The changes are not so marked. The ova are numerous many of them show irregular outline and tendency to vacuolation. The follicular contents are shrunken and the cells of the discus and membrana granulosa are disintegrated. There is a marked fibrous increase in the interstitial tissue.

B. & C. thus illustrate remarkable changes which in C. have reached such a stage as would justify one considering it as one of sterility.

The above was noted, when doing a series of experiments with X. ray, the results of which I have not yet published, but they seem to suggest a possibility of X. ray being used as a means of sterilisation of the unfit in the population without mutilation. (Photographs Nos.48-52.)

EXPERIMENT XVI./

EXPERIMENT XVI.

AFTER REMOVAL of THYROID and ONE OVARY the REMAINING OVARY ACTUALLY LOSES WEIGHT. NO COMPENSATORY HYPERTROPHY TOOK PLACE IN THE FOLLOWING.

BROWN RABBIT weighing 1 Kilo. 850 Grms. was on June 6th anaesthetised and prepared, and Right ovary removed and weighed 0·33 Grms. It was congested and had several projecting and well marked Graafian follicles on the surface.

The animal made a good recovery and was in good health, and in October was again anaesthetised, and both Thyroids removed, each lobe weighed approximately 0·1 Grms. The Rabbit was kept in the incubator all night and made a very good recovery. It was kept six months, during which time it was very healthy, and then killed.

The Left ovary was examined. It only weighed 0·205 Grms. an actual loss of 0·125 Grms. from the weight of the Right ovary. The rabbit when killed weighed 1 Kilo.990 Grms.

MICROSCOPICALLY/

MICROSCOPICALLY.

Right Ovary congested - the tissues have stained well. Comparatively few primordial ova.

Left Ovary. Note particular absence of ova and only very few follicles. The stroma and interstitial cells are well seen, their large nuclei deeply staining. There is an increase of fibrous tissue throughout the stroma. (Photograph No.47.)

SUMMARY/

SUMMARY OF FOREGOING EXPERIMENTS ON HYPERTROPHY OF OVARY.

My results tally somewhat with both those of Bond and of Marshall & Carmichael. For it is evident from my own experiments that in young growing, and full grown animals, compensatory hypertrophy occurs in the remaining ovary after unilateral oophorectomy, and this apart from coitus. Under certain conditions, viz:- old rabbits whose tissues have lost the property of further growth, there is no compensatory increase, - nor is there hypertrophy even in young rabbits, if, in addition to the removal of one ovary - the thyroids are also removed. Furthermore, in young rabbits exposed to certain doses of X.rays, compensatory hypertrophy does not occur, and if the doses are large and the rabbits very young, it would seem that the growth of the ovaries and other glands, viz:- Thyroids and Adrenals, is apparently arrested. In the weights recorded of my three rabbits from the same littler, there is a striking ratio between these glands, particularly/

particularly the ovaries and thyroids, which, in the rabbits A.& B. are 0·03 grms. and 0·035.

This corresponding rise and fall in function or correlation of the ovary and thyroid, is frequently seen clinically and a case reported on February 3rd, 1912, in the Journal of the American Medical Association is typical of Hypothyrodism and Amenorrhea.

Patient had two miscarriages and shortly after ceased to menstruate entirely. She had constant headache, nausea, vertigo, backache and numbness of the extremities. She was dull and sleepy and her skin was dry. No pelvic or blood condition. The Thyroid was scarcely palpable. With Thyroid treatment the menses returned in two months.

On the other hand, I have at present a patient under treatment - Mrs G.H. aged 49, who four years ago had double Oophorectomy and subtotal hysterectomy performed. She suffers from palpitation and headache, but despite the removal of both ovaries - very thoroughly by an experienced and skilful gynecological surgeon, so that no part of the ovary was left - she continued to have the regular loss of blood/

blood and mucous periodically from the cervical stump (menstruation) which was accompanied by backache, and the bleeding has persisted, her last period being on the 6th of this month, and lasted 6 days. It has, at times, been excessive and was so in July of 1912, when the patient complained of breathlessness, headache, nausea, nervousness, cold feet and hands, numbness and tingling in the limbs, insomnia and praecordial oppression. I ordered her Capsules of corpora lutea gr.v.t.i.d., and this quickly arrested the blood discharge: but the praecordial oppression, headache and nervousness persisted. The period did not return till Oct.3rd 1912, and then the patient was very unwell and complained of cold hands and insomnia. Her blood pressure was 170 mm. pulse 84 T.97·8°F. I accordingly ordered her Thyroid Extract gr.2½ twice daily. By the 11th Octr. the blood pressure had fallen to 150mm. & patient was feeling much better, and since then the palpitation &c. have disappeared. The blood loss was also arrested until this period in March.

This then seemed also a case of Hypothroidism, associated, not with suppression but with excessive discharge - though the removal of the ovaries and period of life cannot be excluded.

The/

The Thyroid is the great factor in regulating the Calcium content of the body. It is one of the main factors in the absorption and excretion of Calcium (Waller).

Calcium is lost during menstruation and in the various secretions from the Uterus and Tubes.

IS THIS SALINE SECRETION ESSENTIAL TO HEALTH?

So far as I was able to judge, it is not, for in all my fistulous experiments, the rabbits remained in good health, although some at any rate, of the secretion drained away for months.

Bond says that retained under pressure, it is inimical to health. This I was also unable to corroborate, for not only had I rabbits living over long periods with distended cornua, but actual intra-peritoneal injections of the fluid had no ill effects (EXPERIMENT XI.^{B}A. In Bond's experiment, where he established a utero-peritoneal fistula of considerable size, and drained the fluid into the peritoneum for re-absorption, and noted that the rabbit fell into bad health, one cannot altogether set aside the probability, that through this fistula, it was very easy to get an ascending infection from the vagina to the peritoneal cavity.

From/

From my observations, I would regard the functions of this external secretion as protective and drainage. Protective in that it forms a fluid bed for the ovum, surrounding it and facilitating its passage by capillary flow, down the tube to the uterus and by the same means tends to prevent the ascent of germs from the vagina and uterus to the abdominal cavity& drains away any debris from the uterus towards the vagina. I have not found any evidence that it is nutritive to the individual.

We have seen that there is this external saline secretion, but till now, there is no evidence of any internal uterine secretion. It is held that the uterus depends on the ovary for its stimulus. This does not, in all circumstances, seem clear - for the organ functionates, in some cases, after double oophorectomy; and while this is the case, it does not atrophy. Again, with the removal of the ovaries the production of ova ceases, and the womb primarily exists, to form a bed for the ova and to shed this bed (endometrium) if the ovum is unfertilised. In the act of shedding, there is a certain amount of muscular effort, and the muscle fibres of the uterus are thus kept toned: but when this monthly exercise/

exercise, as it were, is withdrawn (as at the menopause) the fibres atrophy, not so much, may be, from the withdrawal of the ovarian secretion, as from the want of exercise. The fact, that even at the menopause, a uterus with a pedunculated fibroid does not atrophy, because it is kept at work trying to expel the growth, strengthens this contention. It is thus a question, possibly, of acquired specialised association of function, rather than a chemical substance supplied, - and I have been unable to find in the literature any evidence that the exhibition of ovarian extract, after removal of the ovaries in animals had prevented the strophy of the uterus. Certainly in a rabbit, to which I gave corpora lutea and ovarian extract, I found the uterus extremely atrophied. (EXPERIMENT X.A.) (Photograph No. 32.)

The muscularis mucosae degenerates more slowly than the muscle fibres, in cases of double oophorectomy, and this suggests that it may possibly furnish an internal, as well as the external saline secretion. If that be so, then hysterectomy, by removing this, will probably impair health, and in turn injure the organs of associated function, viz:- the ovaries. Contrast the appearance of a rabbit with ovaries/

ovaries removed, which is fat and well nourished, with that of one after hysterectomy with dull coat and tendency to absence of fat.

In pregnancy, the endometrium, does seem to elaborate a secretion which stimulates the growth of the corpora lutea, - why should it not then, in the anoestrous state? If so, then the preservation of any part of this, should be a distinct advantage to the economy.

In the following experiments, the effects of Total and Sub-Total hysterectomy are contrasted and the results given of the attempt to supply any defects of removal by the injection of uterine extract. The general health of the animals and their nutrition, and the condition of the ovaries was observed.

INTERNAL UTERINE SECRETION.

Have we any evidence of this? It occurred to me that if such a secretion existed, some indication of the manner in which it acts, and of its nature, might be afforded by experimentally removing the source of its production (partly or wholly) and supplying it artificially.

How/

How does this secretion influence the ovary?

The fact is established and well recognised, that to ensure the active growth of lutein tissue in the ruptured follicles in the ovary, it is necessary and essential that a fertilised ovum should have become embedded in the endometrium, though my EXPERIMENT XIIa, and some sections in the series, do not support this. This, then, is a direct influence from the uterus to the ovary by way of the blood stream. The blood serum of pregnant rabbits then, should contain the substance elaborated at the site of the trophoblast, and the properties requisite to effect the typical changes of pregnancy in ruptured follicles in the ovaries of rabbits, injected with such serum. To verify this, I performed total hysterectomy in two rabbits, allowed coitus and injected them with the blood serum of pregnant rabbits.

EXPERIMENT XVII./

EXPERIMENT XVII.

PAN HYSTERECTOMY FOLLOWED BY INJECTION OF PREGNANT SERUM.

On August 24th, Two Rabbits believed to be of the same litter were anaesthetised.

A. GREY RABBIT with white collar weight 1 Kilo 620 Grms.

B. WHITE RABBIT with brown spots, weight 1 Kilo 700 Grms.

Both rabbits had the uterus entirely removed, through an incision in the mid-line of the abdomen, with strict aseptic precautions. Healing was rapid by first intention. Coitus was permitted to ensure the rupture of the follicles in the ovaries.

Rabbit A. was given 5 cc. of serum from pregnant rabbit intraperitoneally on August 31st, and again on September 4th. Four days later the Vagina was congested and coitus took place, - 5 cc.'s doses of pregnant serum were given, intraperitoneally at intervals of a week, the serum being taken from rabbits at different stages of pregnancy. Weight on

October/

October 10th 1 Kilo.680 Grms. By this date from date of coitus, normal pregnancy would have terminated. Rabbit was well and showed no ill effects and on October 17th, was given further 5.cc's of pregnant serum. November 20th coitus took place, and afterwards 5 ccs pregnant serum given, - further doses given till December 20th. Again on January 19th, coitus took place, and thereafter, 10 cc's pregnant serum given, coitus again on January 21st. During February coitus frequently took place and pregnant serum was given regularly. On March 5th, ten days after last coitus, the rabbit being healthy, was killed and the ovaries examined. Weight when killed 1 Kilo 670 Grms. This rabbit only seemed fairly nourished and although a young animal, it had not put on much weight. It was, in fact, thin, and had only a little scantily distributed fat.

The Ovaries - Right ovary weighed 0·175 Grammes. Left Ovary weighed 0·170 Grms. - showed several ovarian follicles on the surface of each ovary. Both ovaries were small, and there was no evidence of corpora lutea on the surface, to the naked eye.

RABBIT B. was similarly treated, the whole uterus being removed. Coitus was permitted at intervals, and the animal treated throughout with the pregnant/

pregnant serum intraperitoneally. After each injection, the external genitals seemed congested for a day or so. This animal was killed six months after hysterectomy, and the ovaries examined. It was poorly nourished, and the fat usually found under the skin - in the omentum and throughout the mesentery had disappeared, and that in the lumbar region and pelvis was very scanty.

Weight of Rabbit 1 Kilo 780 Grms. Right Ovary weighed 0·195 grms. Graafian follicles on surface, Left shows two.

MICROSCOPICALLY.

Ovaries show distinct increase of small cells particularly in the subcapsular region. They are otherwise normal.

Note the presence of luteal tissue in the absence of any trophoblast.

EXPERIMENT XVIII./

EXPERIMENT XVIII.

TOTAL HYSTERECTOMY IN RABBITS.

Three Rabbits were taken (Smooth-haired) White with black spots. These animals were of the same age and were kept under similar conditions.

AUGUST 20th. Weights. A. weighed 1 Kilo 470 Grms.
B. weighed 1 Kilo 520 Grms.
C. weigned 1 Kilo 480 Grms.

AUGUST 17th each rabbit was carefully prepared and anaesthetised, and the uterus removed entirely, - healing was aseptic.

The uterus was of greater bulk in A. than in either of the other two. The ovaries were examined at the operations and all showed well marked Graafian follicles - here again the ovaries in A. were, on inspection, bigger than those of B. & C.

I made an extract of the macerated anoestrus uterus - by pounding and expressing uteri and extracting with saline solution - this was sterilised and standardised, so that 10 cc.'s of extract was equivalent to half the uterus. B.& C. were treated with this/

this from time to time. A week after removal of Uterus B. & C. were both given 5 cc.'s of the extract intraperitoneally. The rabbits were both well and slightly heavier than before operation, showing that they had quite recovered from any shock of removal of the uterus.

SEPTEMBER 4th. Both B. & C. rabbits were given a further 5 cc.'s of the uterine extract, and again a similar dose on September 12th, the respective weights being:-

B. 1 Kilo 600 Grms.

C. 1 Kilo 520 Grms.

SEPTEMBER 22nd.

The rabbits were similarly treated and throughout October, November, December, and January, of the following year, uterine extract was given at intervals of about ten days. The rabbits never seemed as full of life, or as well as normally, and contrasted unfavourably with two in the adjoining cage, from which both ovaries had been removed, the coats of the hysterectomy rabbits being rough and the animals, despite good feeding, did not fatten. The wounds in the abdomen had healed by first intention, so that there was no question of sepsis.

JANUARY 20th. The dose of the uterine extract was increased to 10 cc.'s and this was continued at intervals, till February 20th, on which date the animals weighed/

weighed 1 Kilo 870 Grms. and 1 Kilo 750 Grms respectively. The November and December weights had never exceeded 1 Kilo 660 Grms. in the former and 1 Kilo 550 Grms in the latter.

On February 21st the animals were given 15 cc.'s of the Uterine extract, both seemed in better health, but their coats were not glossy nor did they seem well nourished.

On March 5th B. rabbit weighed 2 Kilo 90 Grms. and C. 2 Kilos 20 Grms. They were killed and examined.

The general nutrition was poor and there was almost an entire absence of fat subcutaneously, and very little throughout the mesentery - the perirenal fat was also greatly less than normal, - there was no evidence of any peritonitis. The ovaries were small. Each contained ovarian follicles, but the general appearance of the ovaries was much paler and apparently less vascular than normal They weighed,

B. Right Ovary 0·10 Grms., Left Ovary 0·115 Grms.

C. Right Ovary 0·105 Grms. Left Ovary 0·092 "

MICROSCOPICALLY.

The ovaries show an increase of small cells with deeply staining nuclei, some rounded, others elongated/

elongated oval, also a proliferation and heaping up of the germinal epithelium in some places. Ova and follicles present in various stages. There is no luteal tissue and no evidence of degeneration, unless the small cell increase can be taken as a beginning fibrosis.

These sections show the method of formation of the discus proligerus , from the running together of several fluid spaces,not by a single cleavage in the cells of the membrana granulosa

(Photographs Nos.53,58, & 59.)

EXPERIMENT XIX./

EXPERIMENT XIX.

TOTAL HYSTERECTOMY WITH INJECTION OF NORMAL STERILISED SALINE.

RABBIT. A. of foregoing experiment.

ON AUGUST 20th the Uterus was entirely removed and it was bigger and better developed than either of the uteri of the other two rabbits. It was thus chosen as the one to have sterilised normal saline solution injected intraperitoneally, on the same dates and in the equivalent amounts, instead of Uterine extract given to the other rabbits.

The wound healed rapidly and was aseptic. This rabbit was weighed from time to time. At the date of operation it was 1 Kilo 470 Grms. A month later the rabbit was distinctly out of condition and weighed only 1 Kilo 280 Grms. Normal salt solution was given at intervals throughout October and November, and at the end of November, the weight was 1 Kilo 180 Grms. The rabbit was losing ground and when killed, there was a marked absence of fat. The peritoneal cavity showed no evidence of peritonitis: the ovaries were small and weighed 0·075 Grms. and 0·072 Grms. respectively/

respectively. The stump of the vagina was perfectly healed. The Ovaries showed a few medium sized ovarian follicles on the surface.

MICROSCOPICALLY.

Ovary shows marked increase of small cells with deeply staining, rounded, oval and elongated nuclei. (Stroma Cells).

There are relatively fewer ova than normally, and the condition suggests an early fibrosis. (Photographs No. 54.)

EXPERIMENT XX./

EXPERIMENT XX.

SUB-TOTAL HYSTERECTOMY IN RABBITS.

On AUGUST 20th THREE RABBITS of same age (litter) were taken and anaethestised and the abdomen opened by an incision in the middle line. The uterus was removed above the cervix, thus leaving a little of the lining mucous membrane. The wounds were closed and healed aseptically. RABBIT A. weighed 1 Kilo 600 grammes. RABBITS B. and C. weighed 1 Kilo 550 grammes and 1 Kilo 580 grammes respectively. The Uteri were small and the Ovaries were seen to contain several well developed graafian follicles.

On AUGUST 28th the weights were 1 Kilo 420 grammes and 1 kilo 440 grammes and each rabbit was given 5 c.c's of the Extract of Uteri intraperitoneally, and this was repeated every ten days or so, and a month after operation, the weights were 1 kilo 520 grammes and 1 kilo 550 grammes respectively. During SEPTEMBER, OCTOBER, NOVEMBER and DECEMBER, these rabbits were apparently eating well, but their coats/

coats lacked that brightness and glossiness of a normal healthy rabbit. They were, however, fatter looking than those with the whole carvix removed.

On JANUARY 20th of the following year the dose was doubled, 10 c.c's of the extract of the uterus being given to each. The weights were now 1 kilo 950 grammes and 1 kilo 990 grammes and the animals were eating well.

During FEBRUARY doses of 15 c.c's were given and the rabbits appeared to have fattened, but were dull. Both were killed and examined on MARCH 5th, weights 2 kilo 100 grammes and 2 kilo 150 grammes. On opening the abdomen there was no evidence of peritonitis, and no adhesions. The Ovaries were small, but each showed several (5 to 7) well developed follicles. There was a marked contrast with the rabbits of Experiment XVIII as here one found fat freely distributed throughout the omentum and mesentery, and a large pad of fat in the lumbar regions, and embedding the Kidneys as normally seen; also a fair quantity of subcutaneous fat. The general nutrition was greatly better than in rabbits of Experiment XVIII. (Photographed to show the fat embedding the kidneys.) (No.55.& 56)

The/

The Ovaries weight 0.105 grammes and 0.095 grammes.

The Ovaries of RABBITS B. and C., Experiment XX. were sectioned and show -

MICROSCOPICALLY

. . . . . Ovary shows only slight small celled increase otherwise normal.

There is a tendency to active proliferation of the germinal epithelium with heaping up in some places.

Many ova and follicles are seen.

The gland shows a more healthy condition than seen in Experiments XVIII, XIX. or XXI.

EXPERIMENT XXI./

EXPERIMENT XXI.

RABBIT A. of the foregoing experiment whose uterus was removed above the Cervix on AUGUST 20th.

The Uterus was bigger and better developed at time of removal, than those of the rabbits B. and C., and the ovaries contained 6 or 7 ripening ovarian follicles which showed on the surface.

A week after operation the wound being firmly healed 5 c.c's of sterile salt solution was given intraperitoneally, and from time to time for several months, and on the same date as B. and C. received Uterine extract this rabbit was given an equivalent quantity of the normal salt solution. On AUGUST 20th it weighed 1 kilo 600 grammes and a month later it weighed 1 kilo 360 grammes - here as in the others there was an initial loss of weight and the animal's coat was dull and rough and the animal listless.

During OCTOBER, NOVEMBER and DECEMBER, a gradual making up of the lost weight was noted. On JANUARY the weight was 1 kilo 600 grammes. The amount of saline now given was 10 c.c.

FEBRUARY/

FEBRUARY 20th weight now 1 kilo 750 grammes. The rabbit eats well, but like the others is dull and listless.

On MARCH 5th the animal was killed and examined. Weight 1 kilo 700 grammes. There was no peritonitis or any evidence of disease.

In this animal again there was this deficiency of fat evident, and particularly so in the region of the kidneys where it had entirely disappeared. The omentum and mesentery were devoid of fat, and the pad of fat on which the ovaries rest was very small and scanty, and there was no subcutaneous fat. The ovaries are pale - both show ripening graafian follicles, five or six on the surface in each.

Right Ovary weighed 0·110 gramme. Left Ovary weighed 0 120 grammes.

As in previous experiments they were cut and examined, and showed

MICROSCOPICALLY

Ovary. Here again one sees a great increase of small cells with deeply staining nuclei; but fewer than in Experiment XIX.

The ova and follicles well seen in the various/

various stages.

It is practically a normal ovary. The increase of small cells with deeply staining nuclei - some rounded, - others elongated, - is apparently a great proliferation of the stroma cells.

(Photograph No.57.)

SUMMARY/

SUMMARY OF HYSTERECTOMY EXPERIMENTS.

All were performed on picked rabbits and comparisons made only with rabbits of the same age. All the rabbits seemed to have had their nutrition impaired - it being more noticeable in the cases of total removal, than in those of partial, and again less marked in those in which Extract of Uterus was given. Those treated with pregnant serum gained very slightly in weight, but were poorly nourished.

The evidence of loss of nutrition was the reduction of fat and in some the entire absence even of perirenal fat, viz. after total hysterectomy in which normal saline was injected, and no Uterine extract supplied, it would seem that the fat disappeared in the following order from the various tissues, firstly from the subcutaneous regions, then from the viscera and omentum and mesentery, and lastly from the Kidney bed and pelvis.

In all the cases treated with Uterine extract there was a gain of at least 500 grammes in weight - still the animals were listless and dull. It might be that after removal from the body there was/

was a change in the Uterine tissue used for making the extract, and thus some of its properties were lost. The Ovaries in all cases were small in size and paler, and apparently less vascular than normally but contained ova and follicles. Those in which part of the mucous membrane had been left had most ova & follicles. Those given Extract of Uterus seemed to be the more active, the gemminal epithelium showing proliferation. In the animals in which no Uterine Extract was given there is the increase of small stroma cells referred to. The gain in weight in those animals treated with the Uterine extract as contrasted with the controls treated with normal saline, strongly suggests that the Uterus supplies to the economy a substance or substances which aid nutrition, but that the living action of the organ is necessary to perfect health, as despite the extract given, the animals never had bright glossy coats and were dull and sluggish. It will be noted that in each instance the rabbit selected as the control, viz. that given simply normal saline, was the best developed at the time of operation.

Probably the source of this substance is from/

from the cells of the deeper layers of the endometrium and from the muscularis mucosae, and it might be termed "Uteromucosin".

FOETAL REMAINS RETAINED WITHIN THE ABDOMEN FOR TEN MONTHS WITHOUT ANY APPARENT INJURY TO THE HEALTH OF THE RABBIT.

In the course of my experiments on two occasions I had evidence of how foetal remains may be retained either within the cornu or extruded into the abdominal cavity - for many months - without apparently interfering with the general health of the rabbit.

For example, in May, 1911, A BROWN AND WHITE RABBIT, weight 2 Kilo, 700 Grammes, became pregnant. The pregnancy was well advanced and prior to full time the animal was anaesthetised and the abdomen opened under aseptic precautions. The Right Ovary was removed for the purpose of studying the Corpus Luteum and any compensatory changes that might occur in the left ovary, and the abdomen closed. There were four foetal rabbits in the cornua. Three days later the rabbit gave birth to <u>two</u> foetal rabbits only, but I could still feel

a/

a large swelling in the region of the Left cornu. No more young rabbits were born so far as I could trace but the swelling persisted. The animal was well and remained so for months, and, as the swelling showed no signs of disappearance on March 28th, 1912, I killed and examined it. On opening the abdomen I found the Left cornu greatly distended in two places, one the size of a small orange and the other the size of a hen's egg. Each contained pultaceous cheesy matter and foetal skeletal remains. The Left Ovary was imbedded in adhesions. The Left cornu had a few adhesions, but nothing obvious to prevent the birth of the rabbits. The specimen was photographed (see plate). (Photograph No.60.)

The foetal remains were evidently those of the pregnancy of May, 1911, and had been retained for ten months without any observable injurious effects. Weight of rabbit when killed, 2 Kilo 875 Grammes.

The above struck me as interesting, another similar case of retention in the peritoneal cavity is recorded under experiment VI. of this thesis.

CONCLUSIONS/

CONCLUSIONS AND GENERAL SUMMARY.

(1) That there is the secretion of a watery saline fluid of a low specific gravity, from the lining of the cells of the uterus and tubes which can be demonstrated by double ligation. (Hydrometra - Hydrosalpinx) (EXPERIMENT XI.A.)

(2) That this fluid is continuously secreted and not dependent on the ovarian functions - for hydrosalpinx and hydrometra can be produced after double Oophorectomy. (EXPERIMENT XI.)

(3) That it is not arrested during pregnancy. (EXPERIMENT VII.B.)

(4) That its retention in the distended cornu or tube, does not, from any inherent property cause abortion of an engrafted ovum - but by the mechanical effect - the pressure distension causing reflex stimuli which induce contractions in the Uterus.

(5) That the retention of the fluid under pressure is not the predisposing cause to the formation of adenomata. These over-growths occur where no such distension exists, and are liable to do so from any damage to the endometrium. (EXPERIMENT VI.)

(6)/

(6) That its function is probably that of drainage and protection, and possibly from its nature (containing as it does a large quantity of sodium chloride) the fluid may act as nutritive to the Ovum in its passage through the tube and prior to its becoming firmly embedded. But that prolonged loss, as from an open fistula for months, does not impair nutrition. (EXPERIMENT V.)

(7) That there is no evidence of any inhibition of the growth of lutein tissue in the Ovary from the absorption of the saline fluid. (EXPERIMENT XI.B.)

(8) That it may furnish the fluid for imbibition by the cells of the endometrium and by the cells in the blood vessel walls causing the succulent spongy nature of the mucosae which is thus kept prepared for the embedding of fertilised ova, or when fertilisation does not take place, the fluid helps by vacuolation to separate the swollen cells which are cast off, (menstruation.)

(9) That the atrophy of the Uterus, after removal of the Ovaries is largely one of disuse.

(10) That the two ovaries act as one gland and that removal of one is followed by compensatory enlargement/

enlargement of the other, all the elements taking part in the enlargement. (EXPERIMENTS XII.A., XII.B., XII.C.)

This enlargement is independent of coitus and pregnancy, and can generally be looked for, excepting under special conditions. The conditions preventing hypertrophy noted were:-

(a) In old rabbits where the tissues had probably reached the maximum of growth. (EXPERIMENT XIII.)

(b) In mature rabbits after Successive doses of X.Rays (EXPERIMENT XIV.)

(c) In young rabbits exposed to definite doses of X.Rays as that equivalent to one or two Sabouraud pastilles. (EXPERIMENT XV.)

(d) In rabbits in which the Thyroids were removed as well as the one Ovary. (EXPERIMENT XVI.)

(e) Adhesions round the remaining Ovary by restricting its blood supply hinder hypertrophy.

(11) That careful application of X ray may possibly furnish a means of sterilising (without mutilating) the physically and mentally unfit.

(12) That there is probably an internal secretion from the deep layers of the mucosae (Utero mucosin) which/

which aids nutrition, for there is a distinct interference with the health of rabbits after hysterectomy - and that this is evidenced by the loss of fat - which in turn is less marked in those treated with uterine extract. (EXPERIMENTS XVIII. & XX.)

(13) That in those cases in which a portion of the mucous membrane was preserved (partial hysterectomy) there was less evidence of malnutrition. (EXPERIMENT XX.)

(14) That while there are demonstrable changes in the Uterus after removal of the Ovaries with apparent little effect on general nutrition, there are few detectible changes in the Ovaries after hysterectomy, but the disturbance in general nutrition is more marked.

(15) That while abnormal symptoms after Oophorectomy can be held in check by the administration of ovarian extract, and corpora lútea, the anatomical changes are not retarded, probably because coincident with separation from the body, a biochemical change takes place in the ovary. (EXPERIMENT X.A.)

The changes after Oophorectomy are first seen in the muscular layers of the Uterus which/

which show changes before the mucous lining: probably it is the mucous membrane that is the important part.

(16) That similarly Uterine Extract given after complete hysterectomy distinctly improved the symptoms of malnutrition which supervened, but did not bring about discernible changes in the organs of associated specialised function viz:- the Ovaries. This, as Marshall has pointed out, is to be expected "since the Ovaries are common "to all Metazoa, and the Uterus came into existence much later in the course of vertebrate "evolution."

This seems to me to strengthen my idea, that the Uterine changes which occur when Ovulation is arrested by Oophorectomy, depend to some extent, on the withdrawal of the necessity for uterine contractions, - that is, exercise of the muscular fibres in casting off the debris of menstruation - or in expelling a Foetus at term - it thus being partially a degeneration from disuse.

That it has been clearly shown in the sections of Ovaries of Rabbits I have studied, that the usually/

usually accepted teaching, as to the mode of formation of the cavity and discus in the Graafian follicle, must be reconsidered. It is stated by Schäfer and other authorities -

> "That fluid begins to make its appearance at <u>one</u> place where there is a cleavage between the two strata of cells, and that it gradually increases, and probably is the cause of the growth and bursting of the follicle. That the discus and membrana granulosa are many layers thick - those abutting on the fluid being polyhedral and spherical in shape and loosely packed together - those lining the follicle and round the Ovum, being columnar - and these send fine prolongations of protoplasm through the zona radiata".

The explanation of the process, as seen in my sections, seems to be that - all of the cells of the germinal epithelium are potential ova - some go so far in the life history and remain as stroma cells, others further and become follicle cells, others develop into ova. All are concerned in the fundamental principle of perpetuity and hence sacrifice everything for the advantage of the Ovum.

The/

The follicle cells not being able to go any further, themselves provide food for the ovum by proliferation and produce the solid block of cells round a young ovum. These cells secrete a fluid which determines their own destruction so that some of them break down and are dissolved - the sites of the weakest cells being those first to give way, producing two, three, four, or more spaces which gradually enlarge by the further disintegration of the cells round them, and ultimately coalesce into one big space, having originated from several fluid spaces, not from a cleavage. The liquor folliculi is the medium of interchange,-for the nourishment obtained from the broken down cells - to reach the ovum by the fine protoplasmic communications through the zona radiata to the yolk chamber. The columnar layer of cells being the palissade upon which the discus cells on the one hand and the peripheral membrana cells on the other, rest and beyond which the liquor cannot encroach.

It is this breaking down of the cells in contact with the fluid that gives them the appearance of being loosely packed. As the cavity enlarges by breaking down layer after layer of cells, the fluid pressure/

pressure rises and the wall bulges towards the site of least support, viz:- that nearest the free surface, here, also, the gradually increasing pressure has obliterated the blood vessels. With rupture the ovum escapes surrounded by its discus of cells, which furnish the nourishment, till the ovum becomes embedded, and continue to do so, till the endometrium is sufficiently active and able to take on the nourishment of the Ovum. The endometrium in turn, receives its first stimulus, not from the Ovum, but from the follicle cells, which immediately they were unable to directly nourish the Ovum (at expulsion) took on active proliferation, producing cells of a different type, vix:- luteal cells, and arranging them after the manner of a ductless gland.

The continued growth of the Ovum is still the first care of the follicle cells, (now the corpus luteum,)and, therefore, must be accomplished by way of the blood stream, which, absorbing the secretion of the corpus luteum, conveys the stimulus to the endometrium: this continues till such time as the foetal and maternal blood communication is established. So that a healthy corpus luteum, means correspondingly a firm implantation - and a healthy ovum - and vice versa/

versa, - for the luteal cells and the cells of the ovum are strictly speaking, in this life history, sister cells, both being the stage further advanced of the follicle cells. With active proliferation of the one, we naturally get rapid growth of the other. To carry this a little further - the ovum,(now the foetus,)at its expulsion from the womb,-at birth,-has to anticipate this event, and so has produced within itself - Mammary hormone - the means of stimulating its future source of nourishment, which, conveyed by the blood stream is elaborated in the Mamma causing growth and enlargement of the glandular elements there ready to supply the nourishment. The stimulus, however, to produce the milk, comes probably from the old follicle cells - in some way or other - now corpora lutea of lactation, and these continue to function for a time. Lactation being well established is now able to carry on the nourishment of the child.

During Lactation, the menstrual functions are normally in abeyance, but apt to return in those nursing, whose milk is thin. This, I have, to some extent, proved clinically. During the past two years observing that the Mammary tissue was scanty in Rabbits with small development of luteal tissue, I have administered/

administered Corpora Lutea to several patients, who menstruated during Lactation, and to others with impoverished and scanty milk secretion, to the benefit of both.

The above shows the intimate dependence of the developing ovum and embryo on the ovary.

The Ovary is backed up by an intimate and complicated system of ductless glands; for we find that during pregnancy the Adrenals, Thyroids and Pituitary all enlarge, and this system, by means of the Internal Secretions, is intimately linked with the fundamental principle of the desire to perpetuate the species and protect the individual. At one end of the system, we have the Pituitary, at the other the Uterus and Mammary Gland.

Investigation has shown the wonderful provision made to keep the chain intact, so that when one part ceases to functionate, another takes up the work and when damaged or removed, then compensation is brought about, either by hypertrophy or vicarious function.

Before concluding, I would refer to the enlargement of the Adrenals, Thyroids, and Pituitary, - though not given here in detail - which occurs after complete castration. The enlargement and increased action/

action of the Pituitary (pars intermedia) with increased formation of colloid material, which is found after the removal of the Thyroids (Herring). Also, that after the removal of the Thyroids, as well as one Ovary, compensatory enlargement in the other Ovary was prevented. (EXPERIMENT XVI.)

Again, that in pregnancy, when the special function of the Ovary, viz:- ovulation, is suspended, the Thyroid and Pituitary (anterior lobe) enlarge, and that, furthermore, during this suspension, the endometrium is specially functioning for the nutrition of the developing embryo. That the cessation of the functioning of the endometrium (at full time) is coincident with the onset of lactation, during which, again, ovulation is (normally) suspended.

That this function of lactation is accentuated by the secretion from the Pituitary. (Schäfer & Mackenzie) All tend to point to the elaborate and complicated compensatory and auxiliary chain of the system of interdependence, which exists between the various organs of the body, - through the medium of the internal secretions - and that whatever is removed in this chain, is either compensated for, or tells back on the supporting glands and probably ultimately/

ultimately, on that remarkable structure, the Pituitary, - which is, so to speak, the final court of appeal - for support.

The Pituitary would seem to be the representation, in the higher nervous system, of a centre which governs and controls the internal secretions, through its nerve connections with the various ductless glands, thus regulating the normal healthy metabolism of the body. For instance, as previously stated, castration first tells back on the Adrenals and Thyroids, and then should the Thyroids fail or be removed, the Pituitary comes to the assistance of these glands. (EXPERIMENT XI.A.)

This is a subject that requires much further careful research, to work out definitely the precise associations, but these appealed very strongly to me, when dealing with the specimens of my Experiments.

In conclusion, it would seem, that the lining membrane of the Uterus and Tubes, by its secretions is a distinct advantage to the bodily health, - at any rate from the experimental evidence in rabbits, - and that in all cases, where possible, it should be preserved, in part at least. The practical deduction, in gynecological surgery is, that there are, to my mind, strong/

strong grounds for preserving the Uterus, in all operative treatment on the adnexa, and not to regard it as simply a sac,to be got rid of, when removing the ovaries, for it does not merely play a passive part, but probably supplies secretions to the economy.

Furthermore, that, if hysterectomy is required, then subtotal rather than pan-hysterectomy, should be practised, so far as is consistent with the entire removal of the condition, for which operation has been undertaken, as by this means, some of the mucous lining is preserved.

I recognise that this work is incomplete, and that much wider investigation is necessary, but I hope that this slight contribution to a very wide subject, may justify the time spent on it.

The facts I desire to emphasise finally are:-

1. That the Uterus should always be preserved if possible - otherwise Subtotal rather than Pan-hysterectomy should be practised.

2. That there is a possibility of sterilising the unfit by means of X. ray.

3. And my observation as to the mode of formation of the cavity and discus proligerus in the Graafian follicle.

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